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A CLINICAL SURVEY OF ONE HUNDRED AND EIGHT CONSECUTIVE CASES OF DIABETIC COMA

THOMAS W. BAKER, M.D.
Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN.

Diabetic coma was first reported in the literature as a separate entity in 1828, when it was described by Stosch; it was later (1854) described by von Dusch, of Germany, and Marsh, of Scotland. However, it remained for Kussmaul, of Strasbourg, twenty years later, to give the classic picture, in which he described the characteristic breathing, the *grosse Athmung,* which today bears his name and remains as perhaps the most pathognomonic clinical sign.

Prior to the memorable discovery of insulin by Banting and his associates in 1921 and its successful commercial preparation one year later, diabetic coma presented one of the most hopeless catastrophes of modern medicine. Before 1922 few writers had the courage to review a series of cases of diabetic coma with its disheartening mortality, but with the advent of insulin the situation assumed a right-about-face, and a number of excellent surveys have appeared. Notable among these surveys were those reported by the following investigators: Joslin and his associates [1] (six reports from the clinic of the New England Deaconess Hospital, 276 instances of coma in 228 cases), Bowen and Heki-

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1. (*a*) Joslin, E. P.; Root, H. F., and White, Priscilla: Diabetic Coma and Its Treatment, M. Clin. North America **8**:1873-1919 (May) 1925; (*b*) Diabetic Coma and Its Treatment, ibid. **10**:1281-1306 (March) 1927. (*c*) Joslin, E. P.; Root, H. F.; White, Priscilla; Curtis, W. S., and Adams, H. D.: Diabetic Coma, ibid. **13**:11-40 (July) 1929. (*d*) Joslin, E. P.; Root, H. F.; White, Priscilla; Jordan, W. R., and Hunt, Hazel M.: Diabetic Coma, ibid. **15**:829-868 (Jan.) 1932. (*e*) Joslin, E. P.; Root, H. F.; White, Priscilla; Marble, Alexander, and Hunt, Hazel M.: Diabetic Coma, ibid. **16**:793-827 (Jan.) 1933. (*f*) Marble, Alexander; Root, H. F., and White, Priscilla: Diabetic Coma, New England J. Med. **212**:288-297 (Feb. 14) 1935.

mian [2] (81 instances of coma in 63 cases), Dunlop [3] (45 cases of coma), John [4] (71 cases of coma) and Bertram [5] (186 cases of coma). There is considerable variation in the percentage of recovery in these series; this, I believe, depends largely on such factors as the severity of the infection and other complications which may attend or precipitate coma and the average age of the patients. Another important factor with regard to recovery is the distance that it is necessary for the patients to travel to reach the particular hospital or clinic; this determines the important factor of the time that elapses between the onset of coma and the institution of treatment. Bertram [6] collected the reports of a series of 1,007 cases of diabetic coma cited by 25 authors since the use of insulin was begun and found the average mortality to be 29.1 per cent.

The present report is of a series of 108 instances of diabetic coma in 99 patients. There were 3 deaths from uncomplicated coma (2.8 per cent), 9 deaths from complications after recovery from coma and 5 deaths from complications without recovery from coma. The 3 deaths from uncomplicated coma occurred within two, ten and fifteen hours, respectively, after the admission of the patient to the hospital. The total mortality was 15.7 per cent. This series comprises the consecutive patients with diabetic coma who were seen at the Mayo Clinic from October 1923, when the first patient with coma was treated with insulin, to January 1934. It should be noted that a number of patients were moribund at the time of admission to the hospital. In 10 cases coma had been present for more than twelve hours before the patient was admitted to the hospital, and in 7 of these cases it terminated fatally.

INTERPRETATION OF COMA

In the interpretation of what constitutes coma I am cognizant that if this interpretation were to depend solely on clinical judgment, the factor of the personal equation would assume an all too important rôle. Classification of the clinical condition into a state which has been designated as precoma and a state of coma without strict regard for chemical determinations allows too much ground for variation in clinical judgment. I have therefore included as cases of diabetic coma all cases, except 3, in which the value for the carbon dioxide-combining power of the plasma was 25 volumes per cent or less at the first determination

2. Bowen, B. D., and Hekimian, Ivan: Diabetic Coma: A Report of Eighty-One Instances, Ann. Int. Med. **3**:1104-1111 (May) 1930.

3. Dunlop, L. W.: Some Aspects of Diabetic Coma and Arteriosclerosis, M. J. Australia **2**:533-540 (Oct. 31) 1931.

4. John, H. J.: Diabetic Coma, J. A. M. A. **93**:425-430 (Aug. 10) 1929.

5. Bertram, F.: Die Prognose des Coma diabeticum, München. med. Wchnschr. **2**:1643-1646 (Oct.) 1932.

6. Bertram, Ferdinand: Pathogenese und Prognose des Coma diabeticum. Ergebn. d. inn. Med. u. Kinderh. **43**:258-365, 1932.

after the patient was admitted to the hospital or in which it subsequently fell below this figure in the early course of treatment or following an operation. The 3 exceptions include 1 case (case 69) in which the determination of the carbon dioxide-combining power of the blood plasma was inadvertently omitted on the day the patient was admitted to the hospital, but the patient unquestionably was in clinical coma, as the value for sugar was 840 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 28 volumes per cent after twelve hours of treatment. In a second case (case 81) in which the patient was admitted to the hospital in an unconscious state the value for the carbon dioxide-combining power of the plasma was 28 volumes per cent after 155 units of insulin had been administered by the referring physician. In a third case (case 94) in which the patient was admitted to the hospital in a deeply unconscious state the value for the sugar was 500 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 28 volumes per cent.

The value of 20 volumes per cent for the carbon dioxide-combining power of the plasma has been adopted by some clinics as the dividing line between a state of precoma and a state of coma. The objection to this is that clinical coma occasionally is observed in cases in which the value for the carbon dioxide-combining power of the plasma exceeds 25 volumes per cent, as illustrated by the 3 exceptions which have been cited, and that whenever the alkali reserve of a diabetic patient is less than 25 volumes per cent only energetic or heroic measures will insure recovery. In the era before insulin was used death almost invariably resulted in such cases. In 6 of the 17 cases in which death occurred the value for the carbon dioxide-combining power of the plasma was more than 20 volumes per cent when the patient was admitted to the hospital. These cases would not have been included in this report had I accepted as instances of coma only those cases in which the value for the carbon dioxide-combining power of the plasma was 20 volumes per cent, and the total mortality, instead of being 15.7 per cent, would have been 14.9 per cent.

INCIDENCE OF COMA AMONG DIABETIC PATIENTS

During 1931, 1932 and 1933 approximately 1,800 diabetic patients registered at the Mayo Clinic. Coma was present in 28 of these patients, an incidence of only 1.6 per cent. I feel certain that this is a low incidence of coma and probably is attributable to the fact that only 56 per cent of the patients who were in a state of coma when they arrived at the clinic were from Minnesota. The distance between the clinic and the homes of the majority of the diabetic patients who were under supervision here was usually too great to be undertaken in such an emergency. In a number of cases the diabetic patient who was in

a state of coma when he arrived at the clinic was on his way to Rochester for treatment when coma developed as a result of dietary indiscretion and omission of insulin on the train several hours before the patient's arrival at the clinic. Joslin [1] reported that the incidence of coma among all diabetic patients who were admitted to the hospital was 2.8 per cent, while John [4] reported an incidence of 4 per cent. The recent report by Solomon and Aring [7] of the incidence of diabetic coma among patients who were admitted to a general hospital is interesting. There were 37,438 admissions at the Boston City Hospital in 1933, and 1,167, or 3 per cent, of these patients were admitted in a comatose state. The dwindling incidence of diabetic coma is emphasized by the fact that of the 1,167 patients who were in coma, only 20, or 1.7 per cent, had diabetic coma.

TABLE 1.—*Data on the Chronological and Seasonal Distribution of Diabetic Coma*

Year	Cases	Year	Cases
1922 (3 months)	3	1928	10
1923	19	1929	5
1924	12	1930	5
1925	5	1931	10
1926	7	1932	8
1927	14	1933	10
1922 to 1934			108

Month	Cases	Season	Cases	Month	Cases	Season	Cases
January	13	Winter	25	July	12	Summer	34
February	4			August	16		
March	8			September	6		
April	7	Spring	23	October	10	Autumn	26
May	10			November	12		
June	6			December	4		
1922 to 1934					108		108

Chronological Distribution.—Table 1 illustrates the yearly and seasonal incidence in the 108 cases of diabetic coma. As will be seen, coma occurred more frequently in August than in any other month. August was also the leading offender in Joslin's series.[1e] A larger number of patients were seen in the summer (June, July and August) than during any other season. This possibly may be explained by dietary infractions in the summer, plus the interruption of the diabetic regimen by a vacation. A higher incidence of coma during the winter, when infections of the upper portion of the respiratory tract are numerous, was the expectation, but there were fewer instances of coma in December and February than in any other months.

Distribution According to Age and Sex.—Recent observations and impressions that diabetes is more prevalent among females than males, contrary to earlier reports, is corroborated in this series (fig. 1). Atten-

7. Solomon, Philip, and Aring, C. D.: The Causes of Coma in Patients Entering a General Hospital, Am. J. M. Sc. **188**:805-811 (Dec.) 1934.

tion has been called also to the fact that the predilection for the female is greater among elderly patients and that diabetes is of a more severe grade among elderly women than it is among men of corresponding age.[8] In the 37 cases of coma in which the patients were over 40 years of age, 26, or 70 per cent, of the patients were women.

The average age of the entire group of patients was 31.2 years. The youngest patient was 3 years and the oldest one 74 years of age, respectively. Both of these patients recovered. I have been unable to find an instance of recovery from diabetic coma cited in the literature in

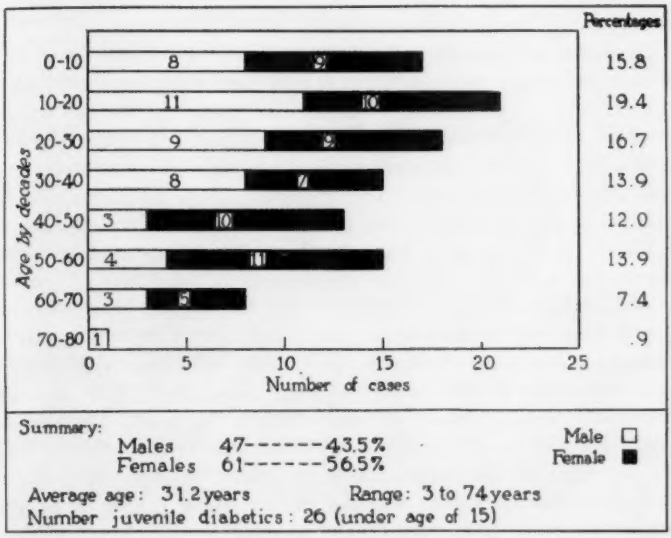

Fig. 1.—Distribution of the patients by age and sex. The distribution according to sex during the first four decades was practically equal, while females predominated among the patients over 40.

which the patient was as advanced in years as was the latter patient. The following is a brief résumé of the clinical history of this patient (case 96):

A man aged 74 years was admitted to the hospital in a stupor. The value for sugar was 469 mg. per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 17 volumes per cent. He previously had not been aware of the existence of diabetes. His condition was complicated by myocardial degeneration, coronary sclerosis and auricular fibrillation. Recent

8. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: I. Characteristics and Trends of Diabetes Mortality Throughout the World, Am. J. M. Sc. **186**:753-773 (Dec.) 1933.

correspondence revealed that now, at the age of 76, his health is good. He has gained 55 pounds (24.9 Kg.) in weight and has not experienced any subsequent coma, despite the fact that he has undergone thyroidectomy in the interim.

The incidence of coma by decades is shown in figure 1, the highest incidence being in the second decade. Twenty-six patients (32 attacks of coma) were children who were less than 15 years of age. The mortality in the first four decades of life was 4 per cent (3 deaths among 71 patients with coma), and in the next four decades it was 40 per cent (14 deaths among 37 patients with coma).

DURATION OF DIABETES BEFORE THE ONSET OF COMA

The onset of diabetes was calculated from two angles: first, from the onset of symptoms, and, second, from the first detection of glycosuria. The average duration of diabetic symptoms before the onset of coma was twenty-six and one-half months, while the average time from the first discovery of glycosuria to the appearance of coma was twenty-three and one-half months. The average patient, therefore, had had diabetes for approximately three months before a diagnosis was made. In 1 case coma developed after the disease was known to have been present for ten years. On the reverse side of the ledger, 13 patients who were admitted in a comatose state had not had any previous knowledge of the presence of diabetes. In 51 per cent of the cases coma had developed within the first year of the disease. The rapidity with which coma may strike without any prodromal symptoms is most alarming. Particularly is this true of diabetic children, in whom the acid-base equilibrium may be upset by an insignificant dietary infraction or infection. It has been the experience in this clinic that the young diabetic patient, the elderly woman and the patient whose disease is of short duration are most frequently subject to coma.

PRECIPITATING FACTORS OF DIABETIC COMA

An interesting phase of this survey is the study of the precipitating factor in the individual case. In the great majority of cases coma can be ascribed to dietary indiscretion, omission of insulin or infection (table 2).

Dietary infractions and omission of insulin have been considered together because these factors frequently are joint perpetrators in precipitating coma. It is also true that most of the 17 cases listed in the group in which no precipitating factor was recorded rightfully belong in group 1. If these two groups are combined, it will be found that in 58, or 53.7 per cent, of all cases coma was the result of the failure of the patient or of the parents of the child to appreciate properly the importance of diet and the administration of insulin. The most striking

example of flagrant disregard for the diabetic routine occurred in case 78. This man, aged 53, was known to have had diabetes for five years. Coma was precipitated by an alcoholic debauch which lasted for three days. During that time little food other than alcohol was consumed, and the administration of insulin was omitted entirely. Another patient (case 16) abandoned the use of insulin for chiropractic adjustments. Thus, it will be seen that ignorance and folly remain the worst enemies of the diabetic patient. However, 16 of the patients could not be held responsible for the coma, as the diagnosis of diabetes had been made only a few days prior to, and in some cases, during the coma.

The significance of infection in precipitating diabetic coma is well known. As Joslin has tersely expressed it, "the diabetic is running in crowded traffic when in the midst of an infection." Infection was the

TABLE 2.—*Data on the Precipitating Factors in Cases of Diabetic Coma*

Group			Cases	Percentage*
1	Dietary infractions and omission of insulin		40	37
	No therapy prior to coma	16		
	Dietary indiscretions and insufficient insulin	24		
2	Infection		32	30
	Respiratory infections	19		
	Pyelonephritis	2		
	Gastro-enteritis (?)	2		
	Appendicitis, cholecystitis, pancreatitis, septicemia, erysipelas, cellulitis and adenitis, rheumatic fever, measles and dengue fever (1 each)	9		
3	Operation (at clinic or elsewhere)		5	5
	Extraction of abscessed teeth	2		
	Cholecystectomy	1		
	Perineorrhaphy	1		
	Biopsy of lymph node (Hodgkin's disease)	1		
4	Miscellaneous and doubtful factors		13	11
	Exophthalmic goiter	6		
5	No recorded factor (cases probably belong to group 1)		18	17
	Total		108	100

* Figures are approximate.

precipitating factor in 32 cases. Predominant are the respiratory diseases, which accounted for more than half the attacks of coma attributable to infection as a precipitating factor. The respiratory diseases varied in degree from acute coryza to pneumonia and postpneumonic abscess. The common cold, with its sequelae, was the offending factor in 7 cases. Pneumonia and influenza were held accountable in 9 cases. Among the other infections listed as causative factors in this series were streptococcic pharyngitis, erysipelas, cellulitis with suppurative adenitis, staphylococcic septicemia, active bilateral pulmonary tuberculosis, acute rheumatic fever, measles, pancreatitis, cholecystitis, appendicitis, dengue fever and gastro-enteritis (?).

In 5 cases the attacks of coma followed a surgical operation. The fact that a minor as well as a major surgical procedure may precipitate coma is well emphasized by the fact that the extraction elsewhere of

abscessed teeth was sufficient in 2 cases to precipitate coma. In a third case (case 92), in a woman aged 66, who previously had been debilitated by an old cerebral hemorrhage, the mere excision of a cervical lymph node for biopsy in Hodgkin's disease was sufficient to produce a change from diabetic balance on the day of operation to profound coma on the succeeding day. The value for sugar reached 560 mg. per hundred cubic centimeters of blood, and the carbon dioxide-combining power of the plasma was 6 volumes per cent. In 1 case (case 65) the attack of coma followed simple perineorrhaphy complicated by postoperative pneumonia. Another case (case 80) in which the attack of coma was attributable to operation represents one of the few cases of insulin allergy noted at the clinic and will be considered later.

On the other hand, it is not unsafe to operate even in the presence of severe acidosis, provided the latter is combated energetically. In 9 cases in the present series a major operation was performed after the patient had recovered from the coma and before his dismissal from the hospital. Twelve minor operations, such as drainage of an empyema or tonsillectomy, also were performed in this group of cases.

Hyperthyroidism was among the miscellaneous group of factors which precipitated coma. The association of hyperthyroidism and diabetes is not uncommon, but sometimes it is a difficult task to ascertain which antedated or precipitated the other and which should be branded as the prime etiologic factor in the individual case. In the great majority of cases in which the patient was suffering from both diabetes and primary hyperthyroidism Wilder[9] and Joslin[10] have found hyperthyroidism to be the antedating disease.

In 6 of the present series of cases of coma hyperthyroidism was of such severity that I feel justified in classifying it as the factor which precipitated the coma. The basal metabolic rates of the patients ranged from +34 to +72. The highest reading was obtained in a patient (case 18) 69 years of age. A second attack of coma developed as a result of a preoperative thyroid crisis while the patient was in the hospital. She previously had experienced coma a short while before she was brought to the hospital. Here is an example of an elderly patient who suffered from three attacks of coma within the space of a few months, all of which were attributable to severe hyperthyroidism. After thyroidectomy there was no further difficulty, and she had no subsequent attacks of coma. The patient finally succumbed to heat prostration at the age of 80. The other 5 patients who were subjected

9. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**:736-760 (Dec.) 1926.

10. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 881.

to thyroidectomy following recovery from coma likewise had an uneventful convalescence, and they report no subsequent coma.

Labbé [11] seems to have been the first to note the striking effect of the administration of iodine on the intensity of diabetes associated with exophthalmic goiter. Wilder and Boothby [12] stressed the importance of the administration of iodine, intravenously if necessary, with insulin in the treatment of coma associated with hyperthyroidism, if a successful outcome is to be expected.

Among the other miscellaneous precipitating causes of diabetic coma in this series were coronary occlusion, intestinal obstruction from carcinoma of the sigmoid flexure, the crisis of pernicious anemia, abdominal trauma (?), emotional upset (?), hemochromatosis and acute yellow atrophy of the liver. The last three require some comment.

That hyperglycemia may result from an emotional crisis is established, but it seems difficult to conceive of a crisis of such extraordinary intensity as to precipitate coma. However, this apparently is what happened in case 26, in which diabetes previously had been well controlled. Coma developed (the value for the sugar was 420 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 11 volumes per cent) soon after the patient had learned of the accidental death of her son. In this connection the interesting case reported by von Noorden [13] comes to mind, that of a bank director who apparently was in good health but who returned home after a stormy session and soon after dinner was found in coma by his valet.

In the case in which coma was attributed to hemochromatosis, the coma is explained by the development of an unusual resistance to insulin. This case has been reported elsewhere by Allan and Constam.[14] The clinical history is a follows:

CASE 63.—A man aged 58 had suffered from diabetes secondary to hemochromatosis for seven months. The diagnosis was established by biopsy of the skin and later was proved at necropsy. On admission to the hospital the patient showed marked pigmentation of the skin, hepatic enlargement which extended 8 cm. below the right costal margin, ascites and dependent edema. Laboratory studies confirmed the presence of hepatic damage. For seventy-four days the intensity of the diabetes varied considerably. The value for the sugar ranged from 106 to 573 mg. per hundred cubic centimeters of blood. The patient finally lapsed into coma. Despite the administration of huge doses of insulin, as much as 800 units

11. Labbé, Marcel: Diabète et goitre exophtalmique, Ann. de méd. **7**:95-103, 1920.

12. Wilder, R. M., and Boothby, W. M.: Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes, J. Clin. Investigation **1**:590 (Aug.) 1925.

13. von Noorden, quoted by John.[4]

14. Allan, F. N., and Constam, G. R.: Insulin Resistance in a Case of Bronze Diabetes, M. Clin. North America **12**:1677-1687 (May) 1929.

being given in a single day, mostly intravenously, the value for the blood sugar was barely altered. The immediate cause of death was infected ascites which produced low grade peritonitis.

The following patient presented a somewhat similar problem:

CASE 84.—A woman aged 33 was admitted to the hospital in profound coma, which had been present for twenty-four hours. The value for the sugar was 320 mg. per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 18 volumes per cent. The patient had been aware of the diabetes for only two days preceding the attack of coma. In all probability this represents a case of acute fulminating diabetes in which the interrelationship between the pancreas and the liver was suddenly and violently disturbed. The patient was deeply jaundiced, and the amount of bilirubin in the serum was greatly increased. There was acute tenderness over the entire right upper quadrant of the abdomen. The test for hepatic function showed dye retention of grade 4. The urine showed positive results for tyrosine, and there was 75 mg. of arsenic in 1,200 cc. of urine. Contrary to the experience in the case of hemochromatosis, the recovery from coma was prompt after the administration of 190 units of insulin, but toxic nephrosis ensued. The value for urea gradually increased from 63 to 222 mg. per hundred cubic centimeters of blood, and death occurred eighteen days after the patient was admitted to the hospital. Necropsy substantiated the diagnosis of acute yellow atrophy and toxic nephrosis and revealed atrophy and a definite decrease in the number of islands of Langerhans.

The recital of these unusual cases, however, should not divert emphasis from the usual triad of precipitating influences in diabetic coma, namely, dietary indiscretion, omission of insulin and infection, which in this series accounted for 90, or 83 per cent, of the 108 cases.

CLINICAL CONSIDERATIONS

Kussmaul breathing, nausea and vomiting, drowsiness or coma, hyperglycemia, ketonemia, glycosuria and ketonuria are the cardinal symptoms and signs of diabetic coma. Later, nausea and vomiting will be considered together with abdominal pain and leukocytosis, and attention will be directed to the confusing similarity which may exist in cases of uncomplicated coma and acute surgical disease of the abdomen.

Kussmaul Breathing.—This is perhaps the most significant clinical finding of impending or present coma; although it is not invariably present. Kussmaul respirations were recorded in 82.5 per cent of the cases in this series. In some cases ketonemia apparently had not reached the stage in which the accessory mechanism of pulmonary hyperventilation as a means of eliminating carbonic acid is called into play. Occasionally, hyperpnea may disappear when the patient is exhausted after it has been present at the onset. This may be interpreted as due to toxic depression of the respiratory center in which the normal response to the stimulation of a lowered alkali content of the blood fails.

Coma.—Coma in the sense of complete unconsciousness was present in 32 cases; stupor, in 32 cases, and drowsiness or marked lethargy, in 41 cases. In 2 cases a normal mental response was present, but these patients lapsed into unconsciousness after they were admitted to the hospital. The historian failed to mention the mental state in 1 case. Death occurred in 7 of the 10 cases in which coma was known to have been present for more than twelve hours before the patient was admitted to the hospital. There seems to be little correlation between the degree of unconsciousness of the patient and the degree of chemical change in the blood. The degree of unconsciousness depends less on the amount of sugar in the blood or the degree of the depression of the alkali reserve than it does on such factors as the presence of infection and the age of the patient. The surprising lack of correlation between the degree of clinical coma and the laboratory data will be considered later. It has been observed that patients between the ages of 12 and 45 years are much more likely to tolerate a decrease in the carbon dioxide-combining power of the plasma without losing consciousness than are very young or very old patients. Infection also predisposes to a lower threshold of consciousness.

The Circulation in Coma.—Studies of the pulse and blood pressure in these cases of coma simply substantiated the observations of many investigators that a patient who has diabetic coma is essentially in shock and that the same remedial measures must often be employed for the two conditions. In 39 cases the pulse rate exceeded 120 beats per minute at the time the patient was admitted to the hospital; the 2 highest rates occurred in cases in which coma was associated with hyperthyroidism. Two patients were pulseless, and auricular fibrillation was present in 3 cases. The value for the systolic blood pressure was less than 90 mm. of mercury in a surprisingly small number of the adult patients. In 32 cases there was some suggestion of cardiac abnormality, which was indicated either in the electrocardiogram or with the stethoscope, but a large number of these irregularities undoubtedly were functional in origin. Circulatory collapse was definitely responsible for the death of 1 patient who probably would have survived uncomplicated coma.

Tension of the Eyeball and Examination of the Ocular Fundus.—The data in these cases unfortunately are inadequate on the subject of the tension of the eyeball. Purves-Stewart [15] expressed the opinion that the lowered ocular tension in cases of diabetic coma is only another manifestation of the general dehydration of the tissues. Joslin [1d] found

15. Purves-Stewart, James: The Diagnosis of Nervous Diseases, ed. 7, London, Edward Arnold & Co., 1931, p. 118.

ocular hypotonia on palpation in 58 per cent of 38 children with diabetic coma. The sign does not signify as poor a prognosis as it formerly was believed to indicate.

The ocular fundus was examined almost as a routine in these cases. It was normal in 78 per cent of the cases, and in only 14 per cent could the changes be ascribed to diabetes. Lipaemia retinalis was present in 7 cases. These results agree roughly with those reported in the recent study by Wagener, Dry and Wilder,[16] in which there was an incidence of 17.7 per cent of fundal lesions among 1,052 diabetic patients. Cataract was present in only 1 case in this series.

DIABETIC ACIDOSIS VERSUS ACUTE SURGICAL DISEASE OF THE ABDOMEN

I have been particularly interested in the frequency with which severe acidosis may mimic acute surgical disease of the abdomen. The diabetic patient who has severe acidosis with abdominal pain, vomiting and abdominal tenderness presents one of the most perplexing problems confronted by either the internist or the surgeon, one which requires the most careful evaluation of clinical and laboratory data. Particularly does this apply to children. The frequency with which this situation arises is more prevalent than has been suspected, as the accompanying statistics will show. To operate in the presence of uncomplicated diabetes is to expose a seriously ill patient to an unnecessary hazard, yet to disregard this triad of symptoms simply because the patient has acidosis is to invite disaster occasionally by neglecting a gangrenous appendix, which may be causing the acidosis. The quandary in which the physician finds himself is not alleviated by the presence of leukocytosis, as will be shown.

The difficulty in making a differential diagnosis in these cases is well illustrated by the following case which previously has been reported in detail.[17]

CASE 41.—A girl aged 9 years had been known to have diabetes for seventeen months. Prior to two weeks before her admission to the hospital the disease had been well controlled. Then an acute colicky abdominal pain had developed with anorexia and nausea. The pain had subsided in two days but had returned a few days later, when it had been associated with vomiting and tenderness over the lower half of the abdomen, especially on the right side, so that the physician had suspected appendicitis and had referred the child to the clinic. On her arrival here she was weak, stuporous and hyperpneic. Definite tenderness and rigidity of the abdomen were not elicited, although the examination was admittedly unsat-

16. Wagener, H. P.; Dry, T. S., and Wilder, R. M.: Retinitis in Diabetes, New England J. Med. **211**:1131-1137 (Dec. 20) 1934.

17. Allan, F. N.: Diabetic Acidosis and Leukocytosis, Am. J. M. Sc. **174**:506-510 (Oct.) 1927.

isfactory on account of the hyperpnea. The value for sugar was 338 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 12 volumes per cent. The temperature was normal. A roentgenogram of the thorax did not reveal any abnormality of the lungs. The number of leukocytes ranged from 59,100 to 66,400 per cubic millimeter of blood; 90 per cent of these were polymorphonuclear neutrophils.

The next morning, after energetic treatment had been employed to combat the acidosis, the patient seemed almost entirely normal. The value for the carbon dioxide-combining power of the plasma was then 30 volumes per cent and that for the leukocytes had fallen to 20,200 per cubic millimeter of blood. The next day it had decreased to 16,000 per cubic millimeter of blood, and a day later it was normal. Recovery was uneventful, but it was thought advisable to perform an appendectomy two weeks later. The pathologic report was "chronic catarrhal appendicitis, grade 1" (on the basis of 4). Correspondence has revealed that no similar attacks of coma have occurred in this case in the succeeding nine years.

This case presented the problem which I have just mentioned. The child obviously had acidosis, but whether or not appendicitis was the precipitating factor in initiating the acidosis was the pressing question. The value for the leukocytes was so great that it was felt that appendicitis, if present, probably had progressed to peritonitis. Largely for this reason, but also on account of the great risk entailed by operation, it was considered best to combat the acidosis vigorously and to await developments. It seems more plausible to ascribe the extreme leukocytosis in this case to the acidosis alone than it does to assume that such a negligible grade of appendicitis was the basis for such severe acidosis.

Another child, aged 12 years (case 35), was suffering from such acute abdominal pain at the time of her admission to the hospital that volvulus was suspected for a number of hours, but the prompt response to treatment with insulin proved the abdominal symptoms to be secondary to acidosis.

While these and other cases show that acidosis alone may often mimic acute surgical disease of the abdomen, there have been others in which acute abdominal disease precipitated the acidosis. The cases reported by Smith [18] are interesting in this respect. A boy, whose story is almost duplicated by the case just detailed, except that the acidosis was not so severe and the tenderness and rigidity of the rectus muscles was more marked, was treated recently at the clinic. The leukocytes numbered 25,000 per cubic millimeter of blood. Operation was performed, and a ruptured appendix with peritonitis was revealed. Although the child had a stormy convalescence, complicated by pertussis, which was present at the time of his admission to the hospital, he finally recovered.

18. Smith, J. H.: Intra-Abdominal Inflammation in Relation to Diabetic Acidosis with Leukocytosis, J. A. M. A. **92**:308-309 (Jan. 26) 1929.

Table 3 summarizes the data in this division of the study. In a number of cases the presence or absence of abdominal symptoms was not specifically mentioned. It is for this reason that two tables of percentages are presented; the first is based on the entire series and the second on the number of cases in which these facts were accurately recorded.

Definite abdominal pain was present in 34 of the 108 cases, or in 41 per cent of the 82 cases in which the presence or absence of this symptom was recorded. In 5 of the 34 cases the abdominal pain could probably be ascribed to the precipitating factor. Empyema of the gallbladder, intestinal obstruction, appendicitis, bilateral pyelonephritis or ruptured esophageal varices secondary to syphilitic hepatosplenomegaly

TABLE 3.—*Data on the Abdominal Symptoms in Cases of Diabetic Coma*

Symptoms	Cases		Percentage*	
	Symptoms Present	Presence or Absence of Symptoms Was Recorded	Based on 108 Cases	Based on Cases in Which Presence or Absence of Symptoms Was Recorded
Abdominal pain	34	82	32	41
From acidosis alone	29			
From other causes	5			
Nausea and vomiting	57	85	53	68
From acidosis alone	40			
From other causes	17			
Leukocytosis, more than 12,000 per cu. mm.	38	69	35	55
From acidosis alone	25			
From other causes	13			
Abdominal pain and vomiting	25	82	23	31
Abdominal pain, vomiting and leukocytosis of more than 12,000 per cu. mm.	16	69	15	23

* Figures are approximate.

were the respective precipitating factors in these 5 cases. Therefore, in 29 cases the abdominal pain could not be ascribed to anything save coma alone. The subsequent course in each case substantiated this diagnosis.

Nausea and vomiting were present in 57, or 67 per cent, of the 85 cases in which the presence or absence of these symptoms was recorded.

The presence of leukocytosis in cases of uncomplicated coma previously has been noted by a number of careful observers.[19] Dehydration has been advanced as a possible cause for it in cases of uncomplicated coma, but the relative constancy of the value for hemoglobin and of the number of erythrocytes does not substantiate this view. More than 12,000 leukocytes per cubic millimeter of blood were present in 38, or

19. Joslin.[1b] Allan.[17] Smith.[18]

55 per cent, of the 69 cases in which a blood count was made at the time the patient was admitted to the hospital. However, in 13 cases, in addition to acidosis, there was some coexistent infection which may have accounted for the increase in the number of leukocytes. Therefore, in 25, or 36 per cent, of the 69 cases in which blood counts were made leukocytosis could be explained by acidosis alone.

While other abdominal emergencies may precipitate diabetic coma, appendicitis must be excluded in the great majority of cases before one can ascribe abdominal symptoms to acidosis alone. Each condition may resemble the other in its early symptoms. Coma is often consequent on appendicitis, either before or after operation. In determining the question of whether or not the abdominal symptoms are dependent on acidosis alone or appendicitis plus a secondary acidosis, only the close cooperation of clinicians and surgeons who have had extensive experience with diabetic patients can assure a high average of successful decisions, and even here errors on both sides of the ledger will inevitably occur. The mental status of the patient, which is dependent on the degree of acidosis present, is often a deciding factor, as the decision may hinge on the degree of cooperation afforded by the patient while the abdomen is being examined.

Just how frequently this perplexing situation arises may be appreciated from the number of these patients who had abdominal pain plus nausea and vomiting and a leukocyte count in excess of 12,000 per cubic millimeter. There were 16 such patients in this series. Many of them came to the clinic with a diagnosis of appendicitis, and in only 5 cases could a coexisting disease which would account for the symptoms be diagnosed. There was an additional group of 9 cases in which abdominal pain, nausea and vomiting were present but in which no leukocyte count was made at the time the patient was admitted to the hospital, thereby making a total of 25 cases in which there was a potential possibility that acute surgical disease of the abdomen was the underlying cause of the coma. However, it is not probable that this last named group of 9 cases caused the clinician any considerable worry from a surgical standpoint, for had this been true, a leukocyte count would have been made. Only 3 of the 25 patients required abdominal exploration—1 for empyema of the gallbladder, 1 for appendicitis and 1 for colostomy for carcinomatous obstruction of the sigmoid flexure. This emphasizes the fact that error, when it occurs, is more likely to be on the side of unnecessary operation; as Smith [18] has said, "anti-ketosis must rank with asepsis in the surgical conscience."

Various hypotheses have been proposed to explain the mechanism of the production of abdominal symptoms in cases of diabetic acidosis. Foremost among them is gastric distention, which undoubtedly often exists. However, it would be enlightening to know how great a part

episodes of subacute pancreatitis play in the cases in which diabetic acidosis simulates acute surgical disease of the abdomen.

DISCREPANCIES BETWEEN CLINICAL AND LABORATORY DATA

Blood Sugar.—Lawrence [20] has reported the highest concentration of sugar in the blood with which I am familiar—2,060 mg. per hundred cubic centimeters. Argy [21] has reported the case of a diabetic Negro who went on a sweetened lemonade debauch, resulting in rapidly fatal coma with the value for the blood sugar 1,710 mg. per hundred cubic centimeters. To Dillon and Dyer [22] goes credit for reporting the

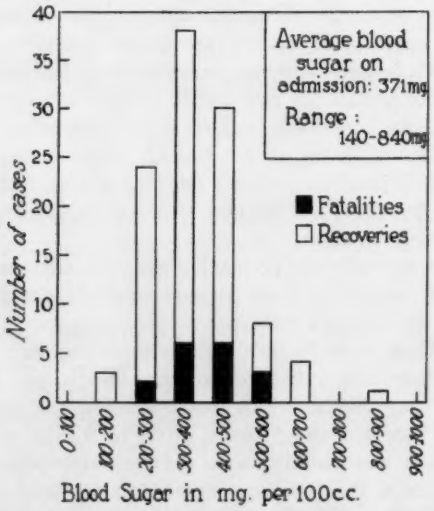

Fig. 2.—Distribution of patients according to the degree of hyperglycemia at the time they were admitted to the hospital. A number of patients who revealed low values for blood sugar had received large doses of insulin prior to the making of the determination.

highest value for the blood sugar in a case of nonfatal coma (1,850 mg. per hundred cubic centimeters). This series of cases is conspicuous for the absence of exceptionally high values for blood sugar. Figure 2

20. Lawrence, R. D.: Extreme Hyperglycemia in Diabetic Coma, Brit. M. J. **1**:377 (March 3) 1934.

21. Argy, W. P.: An Unusal Case of Hyperglycemia (One and Seventy-One Hundredths Per Cent) with Coma, Associated with an Absence of Acetone in the Urine: Report of a Case, Boston M. & S. J. **193**:1236-1237 (Dec. 31) 1925.

22. Dillon, E. S., and Dyer, W. W.: Diabetic Coma with Extreme Hyperglycemia, Am. J. M. Sc. **190**:683-686 (Nov.) 1935.

shows the average value to be 371 mg. per hundred cubic centimeters of blood in this survey. The range was from 140 to 840 mg. At least 15 of these patients had received insulin prior to the making of these determinations. Joslin [1a] has reported 1 case of coma in which the value for sugar was only 130 mg. per hundred cubic centimeters of blood.

I have been particularly impressed with the extreme variability of the values for the blood sugar and the carbon dioxide-combining power of the plasma in cases in which there was deep coma. There seems to be surprisingly little correlation between the laboratory and the clinical data. One patient becomes comatose when the value for sugar is less than 300 mg. per hundred cubic centimeters of blood, while another tolerates hyperglycemia in which the value for sugar is 600 mg. per hundred cubic centimeters of blood and only becomes drowsy. Bruger [23] recently reported a remarkable case in which the patient tolerated 1,500 mg. of sugar per hundred cubic centimeters of blood without the development of coma. Obviously there must be factors which would explain this situation satisfactorily. In an attempt to arrive at the answer to this problem the patients in this series of cases have been classified into three groups. This classification was based on the mental state of the patient at the time of his admission to the hospital. Under the heading drowsy are included those patients who were listless and lethargic and showed no interest in their condition or surroundings; under the term stuporous are grouped those who could be aroused from unconsciousness only by such strong stimuli as shaking or shouting and under comatose are classified those whose degree of unconsciousness was so deep that they could not be aroused by any ordinary stimulus.

The results of the laboratory studies of these groups of patients appear in table 4. It will be observed that there is a difference of less than 100 mg. between the average value for blood sugar of the group classified as drowsy and that of the group classified as comatose. In 8 cases in which the mental state of the patient was designated as drowsy the average value for blood sugar exceeded that of the comatose patients, and conversely, in 10 cases in which the patients were comatose the average value for blood sugar was less than that of the group of drowsy patients.

Two factors seem responsible for this paradoxical situation, namely, (1) the presence or absence of coexisting infection and (2) the age of the patient. From a study of the group of comatose patients in whom the value for blood sugar was comparatively low it was found that,

23. Bruger, Maurice: Diabetes Mellitus and Hyperthyroidism: Report of a Case with a Fasting Blood Sugar of Fifteen Hundred Milligrams per Hundred Cubic Centimeters in the Absence of Coma, J. A. M. A. **104**:2163-2164 (June 15) 1935.

almost without exception, the patients were more than 50 or less than 12 years of age, and in the few cases in which this was not true, coma was complicated by acute and overwhelming infection. Likewise, it was discovered that with only 2 exceptions all the drowsy patients who tolerated a concentration of blood sugar which was higher than that of the comatose patients were between the ages of 12 and 45 years and that little or no infection was present.

Of 95 patients who showed a value for sugar of less than 500 mg. per hundred cubic centimeters of blood, 14 (15 per cent) died. Of 13 patients who showed a value for sugar of more than 500 mg. per hundred cubic centimeters of blood, 3 (23 per cent) died. This difference in the mortality does not seem particularly impressive, and it does not seem that a high value for blood sugar per se is necessarily prejudicial to ultimate recovery from coma. It also was noted that in the 3 cases in which the patient died of uncomplicated coma the values for sugar were only 278, 432 and 519 mg., respectively, per hundred cubic centimeter of blood.

As the value for blood sugar frequently does not parallel the clinical condition of the patient, it obviously is not a reliable criterion on which to judge the severity of the diabetic coma in an individual case. A "laboratory cure" results not infrequently while the patient sinks rapidly; less often the reverse is true.

Carbon Dioxide-Combining Power of the Plasma.—Two patients who at the time of admission to the hospital revealed a carbon dioxide-combining power of only 2 volumes per cent (2.2 and 2.5 volumes per cent, respectively) have been observed. Both patients recovered. Equally low values for this combining power of the plasma have been reported by other writers, but I have been unable to find mention of any case in the literature in which the value was lower than this.

The average value for the carbon dioxide-combining power of the plasma for the entire series was 16.8 volumes per cent (fig. 3). The relation of the carbon dioxide-combining power and the value for blood sugar to the mental state of the patient is recorded in table 4.

In general, unconsciousness is almost always present when the value for the carbon dioxide-combining power of the plasma is less than 12 volumes per cent, but the individual thresholds of consciousness vary greatly. Five patients who disclosed values of less than 12 volumes per cent were classified as only drowsy or stuporous, while 3 patients who showed a carbon dioxide-combining power of 28 volumes per cent were in profound coma. Again, 4 of these 5 patients who tolerated low values for the carbon dioxide-combining power of the plasma without becoming comatose were between 12 and 45 years of age, while con-

versely, the factors of infection and extremes of age explained the degree of unconsciousness in the cases in which the patient was comatose and the alkali reserve was not markedly reduced.

While the value for the carbon dioxide-combining power of the plasma more nearly paralleled the clinical condition of the patient than

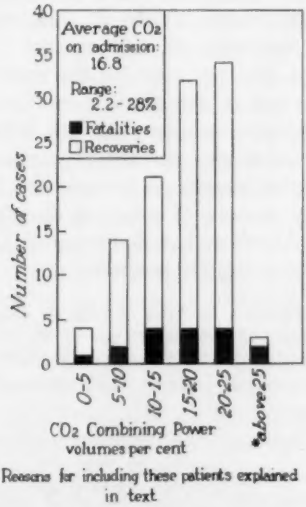

Fig. 3.—Distribution of patients according to the carbon dioxide-combining power of the plasma at the time they were admitted to the hospital.

TABLE 4.—*Correlation of Laboratory Data with Mental State in Cases of Diabetic Coma*

Mental Status	Number of Patients*	Blood Sugar, Mg. per 100 Cc.		Carbon Dioxide-Combining Power of Plasma, Vol. %	
		Average	Range	Average	Range
Drowsy.....	41	330†	188 to 571	21	11 to 25
Stuporous.....	32	363	140‡ to 662	17	8 to 24
Comatose.....	32	423§	222‡ to 840	12	2 to 28‡

* The mental status of 3 patients was not classified.
† In 8 patients in the "drowsy" group the average value for the blood sugar exceeded that of the cases in the "comatose" group.
‡ Insulin was administered prior to the chemical examination which revealed this value.
§ In 10 patients in the "comatose" group the average value for blood sugar was less than that in cases in the "drowsy" group.

did the value for the blood sugar, there was no appreciable difference in the mortality in cases in which the value for the carbon dioxide-combining power of the plasma was more than 15 volumes per cent and that in cases in which it was less than 15 volumes per cent. Death occurred in 7 (18 per cent) of the 39 cases in which the value for the

carbon dioxide-combining power of the plasma was less than 15 volumes per cent, and in 10 (14 per cent) of the 69 cases in which it was between 15 and 25 volumes per cent.

An analysis of the 18 cases in which the value for the carbon dioxide-combining power of the plasma was exceedingly low—10 volumes per cent or less—at the time the patient was admitted to the hospital reveals a most interesting observation (table 5). In this group there were only 3 deaths, or a mortality of 16.6 per cent. If this is compared with the mortality of 15.7 per cent for the entire series, it seems to indicate that the decrease of the alkali reserve of the plasma, once it has decreased to 25 volumes per cent, has little influence on the ultimate prognosis. This situation may perhaps be explained by the fact that there was a comparative absence of infection in these 18 cases (table 5). The presence or absence of infection complicating diabetic coma seems of greater consideration than do the values for blood sugar or the alkali reserve in determining the prognosis.

TABLE 5.—*Results of Treatment in Cases of Diabetic Coma in Which Values for the Carbon Dioxide-Combining Power of the Plasma Did Not Exceed Ten Volumes Per Cent*

Carbon Dioxide-Combining Power of Plasma, Vol. %	Cases	Complications	Recovery	Death
2	2	.....	2	..
3	1	.....	..	1
4	1	Streptococcic pharyngitis.....	1	..
6	1	.....	1	..
7	1	.....	..	1
8	4	.....	4	..
9	4	Exophthalmic goiter in 1 case	4	..
10	4	Pneumonia in 1 case.....	3	1*
Total.....	18		15	3

* This death occurred in the case in which pneumonia was a complication.

Retention of Urea.—The number of cases in which there was an abnormal concentration of urea in the blood without previous evidence of organic renal disease preceding coma places this observation beyond the realm of coincidence. Moderate albuminuria, casts and a few erythrocytes were present in the urine in the majority of cases, but these seemed to be the expression of a pathologic physiology of a temporary nature, which apparently leaves little or no residuum after coma. In 54 cases in this series the value for the urea nitrogen of the blood was determined when the patient entered the hospital. In 27 cases, or exactly half of those for whom this value was determined, there was more than 35 mg. of urea per hundred cubic centimeters of blood. The value for the urea exceeded 50 mg. per hundred cubic centimeters of blood in 17 cases, and in 3 cases it was more than 100 mg. Coma in 2 of the latter 3 cases was uncomplicated by permanent

renal changes; both patients made a satisfactory recovery, while the third patient was the victim of severe cardiorenal decompensation.

The retention of urea in cases of diabetic coma is not always transitory. Occasionally, in a case in which there has been no previous renal damage, the hyperglycemia and acidosis respond promptly to treatment, while the value for blood urea steadily increases as the result of anuria from renal block. Anuria is one of the most serious complications which may follow diabetic coma. It usually appears from twenty-four to forty-eight hours after the onset of coma and frequently after the coma appears to have been controlled. The exact cause of the anuria of diabetic coma is not adequately explained. The following factors have been suggested: (1) circulatory disturbance in the kidney accompanying a decrease of blood pressure and cardiac failure;[24] (2) dehydration of the blood plasma as a result of a lack of intake of fluid, previous polyuria and vomiting;[25] (3) increased endogenous nitrogen metabolism,[26] and (4) actual pathologic change in the renal parenchyma as a result of an excessive excretion of ketone acids and salts and other metabolites in the early stages of coma.[27]

The report of Fullerton, Lyall and Davidson[24] emphasized the gravity of the situation when an increase in the amount of blood urea accompanies coma. They reported 4 deaths in 6 cases of diabetic coma in which the values for urea exceeded 100 mg. per hundred cubic centimeters of blood, and only 1 death in 13 cases in which the values for blood urea were less than this figure. In a recent report from the New England Deaconess Hospital anuria was apparently the cause of 4 of the 6 deaths in cases of diabetic coma and was a contributing factor to death in a fifth case.[1f]

Again, steadily increasing values for blood urea in a case in which there is no previous history of renal disease may be explained by the presence of toxic nephrosis which is secondary to overwhelming toxemia and independent of acidosis. This was true of case 84, in which successive determinations revealed 63, 88, 138, 174, 192 and finally 222 mg. of urea per hundred cubic centimeters of blood as a result of arsenical (?) toxic nephrosis and acute yellow atrophy of the liver.

24. Fullerton, H. W.; Lyall, A., and Davidson, L. S. P.: The Treatment of Diabetic Uraemia with Hypertonic Glucose Solutions, Lancet **1**:558-560 (March 12) 1932.

25. Bulger, H. A., and Peters, J. P.: Concentration of the Blood and of the Urine in Diabetic Toxemia, Arch. Int. Med. **36**:857-873 (Dec.) 1925.

26. Lyall, Alexander: On the Effect of Protein in the Diet of Patients Suffering from Diabetes Mellitus, Quart. J. Med. **20**:115-122 (Jan.) 1927.

27. Snapper, I.: Rôle of the Kidney in Non-Renal Disorders: I. Diabetic Coma Without Ketonuria; II. Coma, Non-Diabetic, with Glycosuria and Hyperglycemia, Proc. Roy. Soc. Med. (Sect. Med.) **21**:73-76 (Sept.) 1928.

Glycosuria and Ketonuria.—Tests for the presence of glycosuria and ketonuria have long been and continue to be among the most valuable and practical tests of diabetic acidosis for the physician to whom determinations of the chemical constituents of the blood are not readily available, but they are by no means infallible. It is well established that the presence of sugar in the urine does not prove the existence of diabetes; at the same time, the absence of acetonuria does not exclude acidosis. The clinician not infrequently is confronted with a patient who is in a comatose state as a result of cerebral hemorrhage and who reveals a moderately high degree of glycosuria and hyperglycemia, whereas, occasionally, a profoundly comatose patient who reveals excessive hyperglycemia will not show any glycosuria.

The highest value for sugar in the urine in this series of cases was 8.75 per cent, and it was noted in a case in which the diagnosis of coma was barely sustained by the clinical and laboratory examinations. In only 41 per cent of the cases in which the level of the urinary sugar was determined quantitatively at the time the patient was admitted to the hospital was the concentration as high as 3 per cent. As a yardstick of the severity of coma, quantitative analyses of the sugar in the urine are in no way reliable.

Ketonuria is almost always noted in cases of diabetic acidosis, but here again the exceptions prove the rule. John,[4] Lemann,[28] Starr and Fitz,[29] Coburn,[30] Argy,[21] Rudy and Levin,[31] Appel and Cooper [32] and others have reported cases of diabetic coma without ketonuria. There were 3 such cases in this series. In most of the reported cases of coma without ketonuria there was usually sufficient clinical or postmortem evidence of renal damage to explain this finding. However, in a considerable percentage of reported cases there was no evidence of coexisting renal changes. In 1 of the 3 cases in this series in which there was no ketonuria but a strong odor of acetone on the breath, coma was complicated by extensive bilateral pyelonephritis, which eventually caused death. Coburn [30] noted that in cases in which there was no ketonuria the patient remained semicomatose until the excretion of ketone acids

28. Lemann, I. I.: Pitfalls in the Diagnosis of Diabetic Coma, M. Clin. North America **9**:959-969 (Jan.) 1926.

29. Starr, Paul, and Fitz, Reginald: The Excretion of Organic Acids in the Urine of Patients with Diabetes Mellitus, Arch. Int. Med. **33**:97-108 (Jan.) 1924.

30. Coburn, A. F.: Diabetic Ketosis and Functional Renal Insufficiency, Am. J. M. Sc. **180**:178-192 (Aug.) 1930.

31. Rudy, Abraham, and Levin, C. M.: Unusual Case of Diabetic Acidosis Without Ketonuria or Ketonemia, New York State J. Med. **27**:1240-1243 (Nov. 15) 1927.

32. Appel, K. E., and Cooper, D. A.: Diabetic Acidosis with Negative Ferric-Chloride Reaction in the Urine: Report of Five Cases, Am. J. M. Sc. **173**:201-220 (Feb.) 1927.

was resumed. In 3 cases in which an indwelling catheter was employed, he noticed that the disappearance of acetone from the urine preceded anuria. Feinblatt [33] has reported an unusual case of fatal juvenile coma in which there was insignificant ketonuria, but large amounts of acetone were present in the spinal fluid. Insulin had no therapeutic effect. Also in the remarkable case described by Argy, in which the value for the blood sugar was one of the highest that has been reported, there was no ketonuria, but a large amount of acetone was present in the spinal fluid.

It is obvious that these patients have acidosis, yet there is no ketonuria or ketonemia, so the ketone bodies cannot be indicted as the cause of acidosis in all cases of diabetic coma. Furthermore Starr and Fitz [29] have shown that in a certain proportion of cases of diabetes mellitus (14 of 114) the amount of undetermined organic acid excreted in the urine was much in excess of the total ketone acids—the reverse of what usually occurs—and that this acid may account for the total organic acids excreted in the cases in which there was no ketonuria. Himwich [34] has recently reported that the unknown organic acid, in addition to the ketone bodies, in the urine of dogs which had diabetic acidosis was lactic acid. It is in these cases that the administration of insulin is seemingly ineffective and the administration of alkalis is advised. Finally, Allen and Wishart [35] in a series of excellent experimental studies on acidosis in phlorhizinized dogs could not discover any parallelism between ketonuria, ketonemia and the amount of sodium bicarbonate in the plasma. They found that death may result with either a high or a low value for sodium bicarbonate in the plasma and with either a large or a small amount of ketone bodies in the blood.

OBSERVATIONS ON TREATMENT

The Use of Insulin.—The timidity which characterized the use of insulin in the years immediately following its discovery is reflected in the fact that the average patient who was treated for diabetic coma at the clinic in 1923 received only 67 units of insulin in the first twenty-four hours after his admission to the hospital, while the average dose in 1931 was 148 units. No definite rules for determining the correct dose of insulin can be formulated, for each patient is truly an individual therapeutic problem. However, there were three factors which seemed of primary consideration in determining the total dose required in the

33. Feinblatt, H. M.: Report of a Fatal Case of Juvenile Diabetic Coma with Insignificant Ketonuria and with a Large Amount of Acetone in the Spinal Fluid, Arch. Int. Med. **34**:508-510 (Oct.) 1924.

34. Himwich, H. E.: The Metabolism of Fever, with Special Reference to Diabetic Hyperpyrexia, Bull. New York Acad. Med. **10**:16-36 (Jan.) 1934.

35. Allen, F. M., and Wishart, Mary B.: Experimental Studies in Diabetes: V. Acidosis in Phlorizinized Dogs, J. Metabolic Research **4**:223-254, 1923.

first twenty-four hours after the patient's admission to the hospital, namely: (1) the age of the patient, (2) the depth of the coma, as measured by the degree of unconsciousness (this is usually more dependent on the duration of coma before the institution of treatment than on the hyperglycemia or the depletion of the alkali reserve), and (3) the presence or absence of infection.

The age factor is emphasized by the fact that the diabetic patients who were less than 15 years of age required an average of 59 units of insulin in contrast to the average dose of 111 units for adults in the first twenty-four hours after admission to the hospital. In a completely unconscious 7 year old child who showed a carbon dioxide-combining power of the plasma of only 9 volumes per cent, coma was relieved by the total amount of only 28 units of insulin. In another child, aged 11 years, who showed a carbon dioxide-combining power of the plasma of only 2 volumes per cent, coma was relieved by the administration of only 70 units of insulin. The average dose of insulin in the first twenty-four hours for the entire group of patients was found to be 97 units, but it must be remembered that a large number of these patients were treated between 1922 and 1925, and it is admitted in the light of present knowledge that they were given inadequate doses of insulin. The extremes of the doses of insulin administered in the first twenty-four hours varied from less than 10 units in an insulin-sensitive person, who fortunately was in a mild coma, to 500 units, which was required by an insulin-resistant patient. It subsequently was necessary to give the latter patient a total of 980 units, mostly intravenously, before the coma was finally relieved.

It has been our experience at the clinic that the degree of unconsciousness is a better criterion in determining the total amount of insulin required to relieve coma than is the value for blood sugar or that for the carbon dioxide-combining power of the plasma, although, of course, the laboratory and clinical data often parallel each other. The average dose of insulin administered in the first twenty-four hours to a totally unconscious patient was 170 units; for a similar condition since 1930 the average dose has been 253 units.

As a matter of comparison, it is interesting to find that in only 6 of the 13 cases in which the value for sugar exceeded 500 mg. per hundred cubic centimeters of blood did the patient receive more insulin in the first twenty-four hours than the average amount for the entire series. Similarly, the amount of insulin required in the first twenty-four hours by the group in which the value for the carbon dioxide-combining power of the plasma was markedly decreased (10 volumes per cent or below) at the time the patient was admitted to the hospital reveals the same lack of correlation. It therefore seems that the degree of unconsciousness of the patient is a factor of greater importance in

determining the total amount of insulin required to relieve coma than the value for blood sugar or the depth of depletion of the alkali reserve. This has also been the experience of Bowen and Hekimian,[2] who said that "this requirement [the dosage of insulin in the first twenty-four hours] did not appear to have any direct relationship to the height of the blood sugar, the carbon dioxide-combining power, leukocytosis or blood urea nitrogen, although we usually expected a patient with extreme hyperglycemia to tolerate more insulin."

The duration of coma before the institution of treatment frequently determines the depth of unconsciousness of the patient at the time of his admission to the hospital. It is generally true that coma which has been present for more than twelve hours before treatment is begun is refractory to insulin, and large doses are required before any appreciable improvement can be detected. This is illustrated by the case of a woman (case 81) who had been unconscious for more than twelve hours before her admission to the hospital. Although 275 units of insulin was administered, there was no improvement, and she died within two hours after her admission to the hospital. There were 10 patients in the series who had been unconscious for more than twelve hours before the institution of treatment. Of this group, only 3 survived; 6 died within from two to fifteen hours after admission to the hospital, while another recovered from coma but died later. Coma of long duration is always a grave prognostic sign. This factor must always be considered in evaluating the mortality in any series of cases of diabetic coma.

The fact that more insulin is required in a case in which coma is precipitated by an acute fulminating infection than is required in a case of uncomplicated coma in which the degree of hyperglycemia is the same is well established and requires no statistical elaboration.

The amount of insulin to be administered within the first twenty-four hours after the patient's admission to the hospital is thus determined by the age of the patient, the degree of unconsciousness, the duration of the coma and the presence of infection. These four factors are of the greatest importance in determining the ultimate prognosis for a patient in diabetic coma.

Immediately after the patient has been admitted to the hospital the values for blood sugar and the carbon dioxide-combining power of the plasma should be determined, but one need not wait for the laboratory data before administering the initial dose of insulin, as no time should be sacrificed in the treatment of a comatose patient. The amount of insulin required for the initial injection can be gaged fairly well by clinical observation and a consideration of the preceding factors. The first dose usually varies between 30 and 100 units; the initial dose

usually is approximately 40 units. As a rule, if no improvement is observed within thirty minutes after the first injection, the same dose is repeated, and smaller doses are administered frequently thereafter. Hypoglycemia is to be avoided, especially in those cases in which circulatory failure is imminent. It is in such cases that the laboratory data become essential. Insulin administered subcutaneously usually suffices, but occasionally it is necessary to administer it intravenously. This is the method of choice in a case in which the patient is shocked severely and the circulation is failing rapidly.

Insulin Allergy.—When encountered in diabetic coma, insulin allergy presents a problem designed to tax the skill of the most ingenious clinician. This occurred in 3 cases in this series, but fortunately the circumstances were such that none of the patients was in immediate danger.

The first patient (case 80) was a woman who had mild diabetes which responded to the qualitative restriction of diet alone. One year before, at the time the diabetes had been discovered, she had experienced a generalized reaction when insulin was administered. A few days prior to her admission to the hospital acute empyema of the gallbladder had developed, and it had been feared that the necessary surgical operation might precipitate diabetic coma. In the few days between her admission to the hospital and the day of operation she was given intradermal tests for several different brands [36] of insulin, but all produced marked local and generalized reactions within five minutes, so that it became necessary to administer epinephrine. A sixth brand of insulin [37] in diluted doses was later tolerated without systemic effects although with marked local irritation of the skin. As was anticipated, acidosis developed the day after operation, the value for the carbon dioxide-combining power of the plasma decreasing to 21 volumes per cent. Desensitization to the sixth brand of insulin was attempted. A dilution of 0.5 cc. of 80 unit insulin with 4.5 cc. of physiologic solution of sodium chloride was made, and this was given in doses of 1 minim (0.06 cc.) at first. This dose was gradually increased thereafter to 25 minims (1.54 cc.) and was administered at frequent intervals. The response to this treatment was as follows: Prior to the operation the value for sugar was 250 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 42 volumes per cent. Treatment was commenced on the day following the operation, at which time the value for sugar was found to be 310 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was 21 and 12 volumes per cent, respectively, on two different occasions. On the regimen of treatment just outlined, the value for sugar decreased to 190 mg. per hundred cubic centimeters of blood and the carbon dioxide-combining power of the plasma increased to 55 volumes per cent. Before leaving the hospital the patient was able to tolerate the undiluted crystalline insulin, although the injection still caused a local reaction.

36. Insulin-Lilly, Lilly's special insulin (prepared from the pancreas of the calf), Insulin-Squibb, Insulin-Stearns and insulin prepared from the pancreas of the sheep.

37. Toronto crystalline insulin.

In a second case generalized urticaria developed after large doses of insulin were administered. In a third case a marked reaction to ordinary insulin occurred, but fortunately special insulin obtained from the pancreas of calves produced no local or general reaction.

Accessory Measures in the Treatment of Diabetic Coma.—The patient in diabetic coma is usually in shock and nearly always shows advanced dehydration. Therefore, it is of prime importance that treatment directed to combat these conditions should be instituted with a minimum of delay.

A subnormal temperature is the rule in a patient in coma, so warmth must be supplied by sufficient blankets and hot water bottles.

Dilatation of the stomach is a frequent accompaniment, and gastric lavage is often desirable. Lavage with from a 2 to 5 per cent solution of sodium bicarbonate has been employed, leaving from 200 to 300 cc. in the stomach. A cleansing enema is desirable. Stimulants are often necessary, and caffeine sodiobenzoate and digitalis must be administered in many cases. The value of iodine in the treatment of diabetic coma complicated by hyperthyroidism has been mentioned.

The dehydration was combated by the administration of physiologic solution of sodium chloride by the subcutaneous, rectal or intravenous route. Fluids were given hourly by mouth in quantities of from 100 to 200 cc. during the first twenty-four hours, provided the coma had been relieved and nausea and vomiting were no longer present. The average total intake of fluid in cases in which this was accurately recorded was 2,658 cc. in the first twenty-four hours after the patient's admission to the hospital. In cases in which the initial value for blood sugar was only moderately elevated but the alkali reserve was markedly decreased, it has seemed to be advantageous to substitute the "10 to 1 solution" (10 per cent solution of dextrose in 1 per cent solution of sodium chloride) for the physiologic solution of sodium chloride usually administered in intravenous infusions. This substitution frequently has been made in cases of threatened renal block. Fullerton, Lyall and Davidson [24] and others have successfully employed a hypertonic solution of dextrose intravenously (as much as 25 per cent dextrose) in the treatment of anuria following diabetic coma.

The Use of Alkalis in Diabetic Coma.—Writers on diabetes appear to be in fair agreement on the treatment of coma, except in the matter of the use of alkalis. Around this much debated question a sharp division of opinion has arisen. Clinical and experimental data support the views of both the proponents and the opponents. Many of the arguments are based on conjecture and opinion, and the truth of the matter is still unsettled.

Starr and Fitz [29] have shown that in a certain proportion of cases of diabetes mellitus the amount of undetermined organic acid (later shown by Himwich to be lactic acid) excreted in the urine is much greater than the amount of ketone bodies. Particularly is this true in cases of severe acidosis without ketonuria in which the decrease in the value for the carbon dioxide-combining power of the plasma is much greater than can be accounted for by the molecular concentration of the acetone bodies in the blood. They have concluded that alkalis are urgently required in such cases, as insulin will not affect the acidosis which is the result of acids other than the ketone bodies. Allen and Wishart,[35] as a result of experimental work on acidosis in dogs, concluded that acetone bodies alone were not responsible for the disorder. Hartman and Darrow [38] reported a comparative study of the composition of the plasma in cases of severe diabetic acidosis and the changes taking place during recovery when the patient had been treated with insulin and physiologic solution of sodium chloride with and without sodium bicarbonate and found that the normal values for the carbon dioxide-combining power of the plasma and the hydrogen ion concentration were restored slowly by the use of insulin and fluids alone, while the administration of sodium bicarbonate with insulin and physiologic solution of sodium chloride provided "a rapid, safe, and complete relief from acidosis." They also commented on the remarkable relief from hyperpnea which follows the administration of alkalis. Bowen and Hekimian supplemented the treatment of coma in 76 per cent of their cases with proctoclysis of 5 per cent solution of sodium bicarbonate. They said that the average patient with diabetic coma "apparently does not require alkalies to make a satisfactory recovery, but it has been our clinical impression that cases respond faster and they are more readily relieved of hyperpnea, which is often distressing, when alkalies are used."

I have found no writer who insists on the administration of sodium bicarbonate as a routine therapeutic measure in the treatment of coma; its use is reserved for certain patients as the indications present.

In the preinsulin era the treatment of diabetic acidosis was almost entirely dependent on the administration of alkali, and in that period alkalis were frequently administered in what now would be considered enormous doses. In 1913 Blum [39] called attention to tetany without disturbance of the amount of calcium and phosphorus in the blood serum which resulted from such treatment.

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38. Hartman, A. F., and Darrow, D. C.: Chemical Changes in the Body Occurring as the Result of Certain Diseases: III. The Composition of the Plasma in Severe Acidosis and the Changes Taking Place During Recovery, J. Clin. Investigation **6**:257-276 (Oct.) 1928.

39. Blum, L.: Symptomatologie und Therapie des Coma diabeticum, Ergebn. d. inn. Med. u. Kinderh. **11**:442-491, 1913.

Haldane and his co-workers [40] showed that when alkalis are administered to a patient with acidosis more acid appears to be liberated. This also was demonstrated to be true of a normal subject. These workers have concluded that the administration of alkalis interferes with the combustion of carbohydrates. Mosenthal and his associates [41] expressed the belief that removing acids from the blood by the use of alkalis may injure vulnerable kidneys because of the resulting irritation.

Joslin and his co-workers have consistently argued the negative side of the issue and have pointed with pride, and well they may, to their low mortality of 12.7 per cent in cases of diabetic coma. None of their patients has received any alkali since 1917. Therefore, in 1929 they stated: "we shall not give alkalies for diabetic coma in our clinic and this advice we shall continue to give to other physicians until those who advocate alkalies report a comparable series of cases with better results than our own. . . ."[1e] I believe it is incorrect, however to attribute their excellent results to the fact that alkalis were not administered. Perhaps these results are more likely attributable to the prompt and energetic treatment and the meticulous attention to detail exerted in the care of comatose patients by the clinicians of the New England Deaconess Hospital. Blackfan [42] likewise has obtained excellent results in the treatment of coma in children without the use of sodium bicarbonate.

The series of cases of diabetic coma reported by Bowen and Hekimian, in 1930, although not as large as Joslin's series, presents the answer of the proponents of alkalis. In their 81 cases of coma (carbon dioxide-combining power not exceeding 15 volumes per cent) sodium bicarbonate was administered by proctoclysis, lavage and occasionally intravenously to 76 per cent of the patients. The mortality was exceedingly low—only 12.4 per cent.

The opinion of Dr. R. M. Wilder and his associates at the Mayo Clinic regarding the use of alkalis has been somewhat neutral, but within recent years it has definitely turned toward the use of alkalis in selected cases. Alkalis are not necessary as a routine measure but are definitely effective in certain cases. Two cases will serve to illustrate this point.

CASE 79.—A boy aged 11 years was admitted to the hospital at 5 a. m. The value for sugar was 380 mg. per hundred cubic centimeters of blood and that for the carbon dioxide-combining power of the plasma was only 2 volumes per cent.

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40. Haldane, J. B. S.; Wigglesworth, V. B., and Woodrow, C. E.: The Effect of Reaction Changes on Human Carbohydrate and Oxygen Metabolism, Proc. Roy. Soc., London, s.B **96**:15-28 (Feb. 1) 1924.

41. Mosenthal, H. O.; Killian, J. A., and Myers, V. C.: Value of Sodium Bicarbonate in Treatment of Diabetes Mellitus, J. A. M. A. **78**:1751 (June 3) 1922.

42. Blackfan, quoted by Joslin, Root and White.[1a]

By 11 a. m., although sufficient insulin had been administered to reduce the value for blood sugar to normal, the value for the carbon dioxide-combining power of the plasma had increased to only 12 volumes per cent. Within the next few hours more insulin was given, together with a 5 per cent solution of dextrose, but this also failed to increase the alkali reserve appreciably, to suppress hyperpnea or to restore consciousness, although the value for blood sugar had remained practically within normal limits for ten hours. It then was decided to administer 300 cc. of a 5 per cent solution of sodium bicarbonate intravenously. The extreme hyperpnea was relieved within an hour, and the mental change was readily apparent. This injection was followed by the oral administration of 3 Gm. of sodium bicarbonate every second hour for three doses.

The administration of insulin promptly reduced the hyperglycemia in this case, but it was totally ineffective in relieving the acidosis or coma. It is therefore logical to assume that this case probably represented one of those in which undetermined organic acid (lactic acid, according to Himwich) is more responsible for the acidosis than are the ketone bodies. In such cases alkalis are not only indicated but may be needed urgently.

CASE 75.—A woman aged 59 was admitted to the hospital at 10 a. m. in deep coma. The value for sugar was 534 mg. per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 13 volumes per cent. On account of distressing hyperpnea it was decided to supplement insulin with sodium bicarbonate intravenously. Accordingly, 400 cc. of a 5 per cent solution of sodium bicarbonate was slowly injected. It was apparent to all observers that the hyperpnea was relieved after only 200 cc. of the solution had been injected. By 2 p. m. the value for sugar was 245 mg. per hundred cubic centimeters of blood, and that for the carbon dioxide-combining power of the plasma was 44 volumes per cent and the patient definitely was out of coma.

In 49 (45 per cent) of the cases in this series alkalis were used, but as 15 of the patients received sodium bicarbonate only by mouth and in almost negligible amounts, only 34 patients (31 per cent) received alkalis in effective doses by lavage, proctoclysis or intravenous administration.

The dose of sodium bicarbonate which was employed was never large enough to provoke any untoward results. More than 500 cc. of a 5 per cent solution of sodium bicarbonate has never been administered intravenously, but this dose frequently has been supplemented by the administration of sodium bicarbonate by proctoclysis or by leaving from 100 to 200 cc. of a 5 per cent solution of sodium bicarbonate in the stomach after lavage. The average total dose of sodium bicarbonate has been from 25 to 40 Gm. This was exceeded in only 5 cases. There is little doubt that many of the objectionable results from the administration of alkalis in cases of diabetic coma can be attributed to overdosage. When this is avoided and a proper selection of cases is made, ill effects are infrequently observed.

I suggest that the following factors are indications for the administration of alkalis in diabetic coma: (1) the presence of distressing hyperpnea; (2) the presence of a deeply depressed alkali reserve, especially when the value for the carbon dioxide-combining power of the plasma is less than 10 volumes per cent, and (3) in the cases in which the administration of insulin is ineffective in elevating the carbon dioxide-combining power of the plasma or in relieving the stupor, although it may be normally effective in reducing the hyperglycemia.

SUBSEQUENT CLINICAL COURSE

Eighty of Joslin's 276 instances of diabetic coma occurred among 33 patients who had had two or more attacks of coma. Ralli and Waterhouse [43] have reported the case of a 16 year old girl who finally succumbed to coma after having been admitted to the hospital 19 times because of either marked acidosis or coma. Patients who have had frequent attacks of coma will be found in any large series of cases. Fifty per cent of the 82 patients in this series who were traced had experienced other attacks of coma either before or subsequent to their initial visit to the clinic. One patient survived five attacks of coma only to succumb to the sixth.

Children, for obvious reasons, more frequently have repeated attacks of coma than do adults. Six of the 9 patients who were treated at the clinic more than once for coma were children.

The second attack of coma is likely to be of a more severe grade than the first. More than twice as much insulin was required in the first twenty-four hours of the second attack than was required in the same period in the first attack in the 9 cases in which the patients had more than one attack of coma. Likewise, the value for blood sugar when the patient was admitted to the hospital was higher in the succeeding attack that it was in the first attack in 7 of these 9 cases.

ULTIMATE PROGNOSIS AND CAUSE OF DEATH

Thirty-nine of the 99 patients who comprise this series have died, 50 were living at a recent date and 10 could not be traced. The 39 deaths comprise the 17 patients who died at the hospital and the 22 who died elsewhere from one week to eleven years after leaving the clinic.

Thirty of the 50 living patients rate their health as excellent; 20 say that it is fair. Few of these patients have suffered from acute illnesses other than the diseases of childhood. A few have undergone operations. One patient was reported to have died from "spinal

43. Ralli, Elaine P., and Waterhouse, Alice M.: Diabetic Coma Occurring Nineteen Times in the Life of a Patient with Diabetes Mellitus, J. Lab. & Clin. Med. **18**:1119-1127 (Aug.) 1933.

meningitis," but in view of the fact that he was suffering from active pulmonary tuberculosis when under observation at the clinic, it seems more probable that he succumbed to tuberculous meningitis. This apparently was the only patient in the entire series who had active tuberculosis either before or after an attack of coma. This is in marked contrast to the experience reported by Root,[44] of Joslin's clinic, who found that 8 per cent of the patients who recovered from coma revealed evidence of tuberculosis within three years. Wilder[45] has reported that the records of 3,793 consecutive cases of diabetes mellitus at the Mayo Clinic showed active tuberculosis in only 37, an incidence of less than 1 per cent.

TABLE 6.—*Causes of Death in Cases of Diabetic Coma*

	Fatalities in Hospitals in Rochester	Fatalities Elsewhere	Total
Uncomplicated diabetic coma	3	8	11
Cardiovascular disease	4	1	5
Pneumonia and its complications	2	2	4
Bilateral pyelonephritis with metastatic abscesses	1	..	1
Septicemia	1	..	1
Erysipelas	1	..	1
Acute yellow atrophy and toxic nephrosis (arsenical ?)	1	..	1
Hodgkin's disease	1	..	1
Hemochromatosis	1	..	1
Diabetic gangrene	1	..	1
Advanced pernicious anemia and coma	1	..	1
Carcinoma (sigmoid flexure)*	..	1	1
Meningitis, tuberculous (?)	..	1	1
Acute pancreatitis†	..	1	1
Addison's disease†	..	1	1
Intestinal hemorrhage from unknown cause	..	1	1
Heat prostration	..	1	1
Cause unknown	..	5	5
Total	17‡	22	39

* Diagnosis confirmed by operation at the clinic.
† Diagnosis verified by necropsy elsewhere.
‡ Diagnosis verified by necropsy in 14 cases.

The causes of death in the cases in which coma proved fatal are given in table 6. The clinical diagnosis was confirmed by necropsy in 14 of the 17 cases in which death occurred at the clinic, and either by necropsy or operation in 3 of the 22 cases in which death occurred elsewhere. It will be seen that uncomplicated diabetic coma was responsible for 11 deaths, 8 of which occurred after the patient had left the clinic. In the majority of cases of uncomplicated coma in which death occurred elsewhere, the patients were elderly, and it is likely that cardiovascular disease may have played more of a lethal rôle than the

44. Root, H. F., quoted in Joslin, E. P.: A Diabetic Manual for the Mutual Use of Doctor and Patient, Philadelphia, Lea & Febiger, 1934, p. 125.

45. Wilder, R. M.: Diseases of Metabolism, in Musser, J. H.: Internal Medicine: Its Theory and Practice in Contributions by American Authors, ed. 2. Philadelphia, Lea & Febiger, 1934, pp. 993-1002.

figures reveal. However, cardiovascular disease was listed as the cause of death in only 5 cases. Pneumonia and its complications were responsible for 4 deaths, but the mortality probably is no higher than would have been noted in a similar group of nondiabetic persons. Diabetic gangrene, hemochromatosis, acute pancreatitis and Addison's disease were each responsible for 1 death; but with these exceptions, the other causes of death bore no relationship to diabetes, and the deaths resulted from a wide variety of diseases.

SUMMARY

One hundred and eight instances of diabetic coma in 99 patients who were seen at the Mayo Clinic between October 1923 and January 1934 are reviewed. In all except 3 of these cases the value for the carbon dioxide-combining power of the plasma was 25 volumes per cent or less when the patient was admitted to the hospital. There were 17 deaths, or a mortality of 15.7 per cent in the 108 cases. The mortality in the first four decades of life was 4 per cent; in the next four decades, 40 per cent. Only 3 patients died of uncomplicated coma. Death in these cases occurred within two, ten and fifteen hours, respectively, after the patient's admission to the hospital. The largest number of cases of coma occurred in the summer months, and more occurred in August than in any single month. Among the patients who were less than 40 years of age the distribution by sex was practically equal, but 70 per cent of those over 40 years of age were women. One patient, aged 74, recovered. The average duration of diabetic symptoms before the onset of coma was twenty-six and five-tenths months. In 51 per cent of the cases coma developed in the first year of diabetes.

The factors precipitating the diabetic coma have been determined. Dietary infractions, omission of insulin and infection were the precipitating factors in 83 per cent of the cases. The value of the Kussmaul type of breathing, the degree of unconsciousness, the state of the circulation and the ocular findings in coma are discussed. The frequency with which the symptoms of uncomplicated diabetic acidosis may simulate those of acute surgical disease of the abdomen is revealed. Illustrative cases are reported.

There is a surprising lack of correlation between the value for blood sugar and that for the carbon dioxide-combining power of plasma with the severity of the coma. The ultimate prognosis and the amount of insulin required to relieve coma are more dependent on the age of the patient, the degree of unconsciousness, the duration of the coma and the presence of infection than they are on the data obtained on laboratory examination. The 2 patients who showed a carbon dioxide-combining power of the plasma of only 2 volumes per cent recovered.

The gravity of a high concentration of urea in the blood and anuria in diabetic coma is emphasized. Three cases in which ketonuria was absent are reported.

The treatment of coma as conducted in these cases is described. The indications for the administration of sodium bicarbonate are given. Allergy for insulin presents a serious complication. It was present in 3 patients. In this series 22 have died since leaving the clinic, which, with the 17 patients who died in the hospital, gives a total of 39 deaths in the entire group. The causes of death here and elsewhere are enumerated. Coma, cardiovascular disease and pneumonia accounted for more than half of them. Conspicuous for its absence was tuberculosis, which was a complicating disease in only 1 case; of the 50 patients known to be living, none has any knowledge of having tuberculosis.

SYNCOPE AND CONVULSIONS DUE TO A HYPERACTIVE CAROTID SINUS REFLEX

DIAGNOSIS AND TREATMENT

SOMA WEISS, M.D.

RICHARD B. CAPPS, M.D.

EUGENE B. FERRIS JR., M.D.

AND

DONALD MUNRO, M.D.

BOSTON

For many years it has been known that pressure over the vagus nerve produces slowing of the heart.[1] Not until 1923, however, was the true mechanism of this phenomenon recognized. Hering [2] conclusively demonstrated in animals that slowing of the heart and other effects of such pressure are due to reflexes arising in the carotid sinus. His work has been amply confirmed, particularly by Heymans.[3] The application of these findings to man has been rather recent. A report of fifteen cases by Weiss and Baker [4] demonstrated that an abnormally sensitive carotid sinus mechanism can be responsible for attacks of unconsciousness and convulsions and that such attacks can be reproduced by pressure over one carotid sinus. In most of the fifteen patients the attacks were associated with cerebral anoxemia resulting either from cardiac asystole or from a primary reflex depression of the blood pressure. In two patients, however, unconsciousness occurred in the absence of change in either the heart rate or the blood pressure. We

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Waller, A.: Experimental Researches on the Functions of the Vagus and the Cervical Sympathetic Nerves in Man, Proc. Roy. Soc. London **11**:302, 1860-1862. Czermak, J.: Ueber mechanische Vagus-Reizung beim Menschen, Jenaische Ztschr. f. Med. u. Naturwissensch. **2**:384, 1865-1866.

2. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

3. Heymans, C.: Le sinus carotidien et les autres zones vasosensibles réflexogènes, Paris, Presses Universitaires de France, 1929.

4. Weiss, Soma, and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Rôle in the Causation of Fainting and Convulsions, Medicine **12**: 297, 1933.

have recently reported studies of twenty-one cases of that type.[5] A more detailed account of the various symptom complexes and hypersensitive carotid sinus reflexes in man, which have come to be known as the carotid sinus syndrome, can be found in these reports.

THE CAROTID SINUS SYNDROME

According to present knowledge, a hypersensitive state of the carotid sinus reflex may produce unconsciousness, convulsions or milder manifestations, through one or more of three main reflex arcs. Broadly speaking, both the afferent and the efferent arm of these reflex arcs lie within the confines of the autonomic nervous system. The afferent, or sensory, limb is probably always the same, but the motor pathway differs in various subjects. The stimulus originates chiefly in the bulbous dilatation at the bifurcation of the common carotid artery, known as the carotid sinus.[2] This stimulus may take the form of a stretch by distention from within the artery or of a relaxation by shrinkage of the arterial content. Frequently, hormones or other chemical substances act as powerful stimuli on the remarkably sensitive end-organs within the arterial wall. Furthermore, it is probable that end-organs capable of receiving these specialized stimuli are also present in adjoining parts of the arterial wall and may even occur in other blood vessels. Impulses which result from such stimuli then travel centrally along a variety of pathways to the medulla. The chief afferent pathways are the intercarotid, the glossopharyngeal and the hypoglossal nerves, as well as the vagus nerve and the cervical portion of the sympathetic chain.[6] On reaching the brain stem the sensory impulse traverses the central synapses and after crossing passes contralaterally as a motor impulse toward the periphery through rather widespread autonomic nerve pathways. It is the variation in the peripheral distribution of the abnormally powerful motor impulses, with the resultant activity, that differentiates the types of symptoms included in the carotid sinus syndrome.[5] The type of response elicited by the stimuli traveling over the nerve pathways depends, then, primarily on the location of the motor responses induced. In man the three motor pathways responsible for syncope involve the vagus nerve, the vasomotor-depressor nerves or the central motor pathways. They also commonly appear in a mixed form, and the type of syncope is then classified in accordance with the dominant motor pathway involved.

5. Ferris, E. B., Jr.; Capps, R. B., and Weiss, Soma: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions: A Study of Thirty-Two Additional Cases, Medicine **14**:377, 1935.

6. Braeucker, W.: Das pressorezeptorische Nervensystem und seine praktische Bedeutung in der Chirurgie, Beitr. z. klin. Chir. **158**:309, 1933.

In normal subjects mechanical stimulation of the carotid sinus does not produce symptoms, and physiologic stimulation induced from within the sinus by varying the intrasinusal pressure produces a specific effect, namely, a slight and temporary change in the peripheral blood pressure. In patients in whom the carotid sinus reflex mechanism is abnormally sensitive, however, mechanical stimulation causes marked symptoms, and intrasinusal stimulation induces many symptoms in addition to the specific effect on the blood pressure. Likewise, chemical stimulation of the sinuses of such patients induces abnormal manifestations. Thus an abnormal response of the carotid sinus may be brought about by one of several stimuli and may take one of several forms. Abnormal afferent impulses may arise from the carotid sinus as the result of normal stimulation in instances in which the sinus is hypersensitive. Furthermore, normal afferent impulses from the sinus may set up abnormal reactions as the result either of changes in the threshold of the central synapses or of increased sensitivity of the motor arm of the reflex arc resulting from disease. Any combination of these three factors may play a rôle in individual cases. The observations reported previously [7] reveal that a hyperactive carotid sinus reflex may be either unilateral, involving one sinus only, the activity of the other reflex remaining normal, or bilateral. If the reflexes of both carotid sinuses are hyperactive, the degree of sensitivity usually differs.

The motor pathways taken by impulses from the carotid sinus may be diverse in abnormal conditions. We have been primarily interested in the motor responses that induce fainting, that is, the vagal, depressor and central responses. In the fifty-two patients [8] studied we encountered, however, a number of motor manifestations causing symptoms not directly related to syncope. These manifestations accompanied the spontaneous attacks and could be reproduced by mechanical stimulation of the carotid sinus. The signs and symptoms produced in our patients are listed in detail in table 1, in the order of their frequency.

The Three Types of Carotid Sinus Syndrome.—As previously pointed out, the dominant motor pathway of a hypersensitive carotid sinus reflex determines the classification of the condition as of one of three types. The first is the vagal type, in which the symptoms, particularly the dizziness, fainting and weakness, result from cardiac asystole. The asystole is due either to sinu-auricular or to auriculoventricular block, which in its turn produces acute cerebral anoxemia. In its pure form the efferent response travels over the vagus nerve to set up a heart block. Associated with it is a fall in blood pressure. An attack with all its characteristics can be reproduced by firm pressure and

7. Weiss and Baker.[4] Ferris, Capps and Weiss.[5]

8. This series does not include the fifteen cases reported by Weiss and Baker.[4]

massage for from fifteen to thirty seconds over the sensitive sinus at the bifurcation against the transverse processes of the cervical portion of the spine. Only one sinus should be stimulated at a time, and the test should preferably be performed with the patient sitting or standing. The attack can be abolished within three minutes by the intravenous administration of 1 mg. of a solution of atropine sulfate, which paralyzes the vagal endings, thus preventing reflex cardiac slowing. Eight minims (0.5 cc.) of a solution of epinephrine hydrochloride administered subcutaneously prevents the attacks, through its local stimulating effect on the ventricles.

The second, or depressor, type of carotid sinus syndrome is the least common of the three and usually appears in association with one of the other two types. Indeed, we have observed it in pure form only twice.

TABLE 1.—*Signs and Symptoms in Patients with the Carotid Sinus Syndrome*

Symptom	Frequency			
	Entire Group	Cerebral Type	Vagal Type	Depressor Type
Fainting	52	33	17	2
Dizziness and weakness	52	33	17	2
Hyperpnea	48	30	17	1
Pallor of the face	48	29	17	2
Bradycardia (slight to moderate)	26	24	0	2
Bradycardia (asystole)	17	0	17	0
Numbness and tingling of the extremities	25	16	9	0
Convulsions	24	11	13	0
Drowsiness	13	9	4	0
Catapiexy	9	8	1	0
Epigastric distress	8	7	1	0
Nausea	7	5	2	0
Lacrimation	5	5	0	0
Cough	4	1	3	0
Amnesia	3	3	0	0
Palpitation	3	3	0	0

The afferent impulse is set up, as in the vagal type, from the carotid sinus, while the efferent impulse acts on small blood vessels by way of the aortic depressor nerves. The symptoms result from primary reflex vasodilatation and secondary depression of the blood pressure, entirely unrelated to cardiac slowing or any form of cardiac arrhythmia. The clinical manifestations are brought about, nevertheless, by cerebral anoxemia resulting from a diminution in the flow of blood to the brain. Spontaneous attacks can be reproduced in the same manner as in cases of the vagal type of syncope. Atropine, however, has no effect on the signs or symptoms, since they do not result from cardiac slowing. On the other hand, epinephrine in the dosage previously mentioned promptly aborts the attack, through its constricting action on the small blood vessels.

The third type of carotid sinus syndrome is the cerebral type. In it the symptoms result apparently from impulses which travel directly to the brain. No significant change occurs in the heart rate or the blood

pressure, and the total flow of blood through the brain is normal during the phase of the attack in which the patient is unconscious.[5] As in the other types, the afferent impulses arise in the carotid sinus. Evidence suggests that these impulses travel to the medulla and are distributed from there as motor impulses directly to certain vegetative centers in the region of the hypothalamus or to the blood vessels which supply such areas. Attacks can be reproduced as previously described, subjective rather than objective findings being prominent. The attacks may be induced within as short a period as five seconds. Neither atropine nor epinephrine aborts or relieves the cerebral type of attack. Treatment of the sinus with procaine hydrochloride, however, makes the local stimulus ineffective.

Clinical Manifestations.—Attacks of unconsciousness, with or without convulsions, which occur at intervals varying from days to months are the commonest complaint. The attack is usually preceded by sensations of dizziness, weakness, ringing in the ears or epigastric distress, but occasionally there are no premonitory symptoms. Between attacks of syncope most patients experience frequent milder attacks which consist of dizziness, weakness or sensations of numbness and tingling of the extremities. The symptoms almost always occur when the patient is in the upright position and are relieved by his lying down when premonitory symptoms occur. The attacks may be related to such factors as sudden movements of the neck, pressure against or blows on the neck and sudden changes in position of the head from horizontal to vertical or vice versa. Factors such as fatigue, emotional upsets and menstruation may precipitate the symptoms. In many cases, however, no such cause can be ascertained. Unconsciousness lasts from one to three minutes, and the patient feels well after recovery, except for headache or continued dizziness in rare instances. In only one case did we observe that the patient felt weak for about a day following both a spontaneous and a single induced syncope. In this case the unique observation was made that in spite of cardiac slowing the arterial blood pressure was elevated after the syncope. There was a striking resemblance between the postsyncopal state of the patient and the condition of a patient under the effect of large doses of epinephrine.

Biting of the tongue and incontinence of urine have each been observed only once. Hyperpnea is usually associated with an attack, but apnea may occur. Nausea with actual vomiting occurred in one patient after stimulation of the carotid sinus. The symptoms which may be associated with attacks are presented in table 1. All these symptoms, once they have occurred in an attack, can be regularly elicited later by pressure over the carotid sinus. Depending on the intensity of the stimulus, mild or severe manifestations can be elicited and their

progress stopped at almost any stage by discontinuing the stimulation. When an attack is induced by the application of pressure to one sinus, pallor of the face as a rule precedes unconsciousness. When convulsions occur they usually begin first in the extremities contralateral to the sinus being stimulated and then become generalized.

Local lesions of the sinus or general disease was found in the majority of our patients (table 2). Of particular interest in this connection is the fact that seven of the seventeen patients subject to the vagal type of syncope there was clinical evidence of degenerative change in the heart, and in the group as a whole there was a high incidence of generalized cardiovascular change.

Four cases of digitalis intoxication were encountered associated with spontaneous and induced attacks. The sensitizing effect of digitalis on the carotid sinus reflex is of considerable importance from a clinical point of view, as we have previously pointed out.[5] When digitalis is administered to elderly patients with coronary disease who complain of spells of weakness or dizziness, on the false assumption that such symptoms are due to cardiac failure, it is likely to aggravate their symptoms. Furthermore, from a theoretical point of view the routine preoperative use of digitalis to prevent cardiac failure is contraindicated unless there is definite evidence of failure. The use of this drug in combination with the administration of volatile anesthetics and the usual manipulation about the neck coincident with anesthesia is likely to be responsible for such operative complications as temporary vasomotor collapse, cardiac arrhythmia or sudden death.

Various grades of neurosis were manifest in several patients. Nine appeared to have a mild type, which was classified by us as neurasthenia. Others showing neurotic stigmas proved to have a low basal metabolic rate not due to hypothyroidism.[5] In one of six patients suffering from definite severe neurosis the basal metabolic rate was 0 per cent, and it ranged from minus 17 to minus 25 per cent in the other five. In general, the vagal and the depressor type of syncope predominate in patients having degenerative disease, and these two types are equally distributed in patients having neurosis. Mild neurosis is frequently present in patients subject to the cerebral type of syncope. The similar behavior of the carotid sinus reflex mechanism in patients with organic disease and in persons with visceral neurosis is of much interest, as it demonstrates the fact that often for identical clinical manifestations the same physiologic mechanism may be responsible in instances of organic and functional disease.[9]

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9. Weiss, Soma: The Interaction Between Emotional States and the Cardiovascular System in Health and in Disease, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 1181.

DIAGNOSIS

The diagnosis of carotid sinus syncope is applied to short attacks of syncope and related manifestations which usually develop when the patient is in the upright position and which can be reproduced with regularity by means of mechanical stimulation of the carotid sinus. Treatment of the sinus with procaine hydrochloride abolishes the effects of stimulation.

Both sinuses should never be stimulated simultaneously. If the response is sufficiently abnormal, a typical reaction occurs after from five to thirty seconds of pressure on one sinus. Improper technic in the execution of the pressure and massage has been, according to

TABLE 2.—*Diseases of Thirty-Six Patients with the Carotid Sinus Syndrome and the Age Distribution of Fifty-Two Patients*

	Entire Group	Cerebral Type	Vagal Type	Depressor Type
Disease				
Local abnormality in the region of the carotid sinus	31	19	10	2
Dilated sinus	21	11	8	2
Cervical adenitis	17	14	3	0
Recurring cervical adenitis	4	3	1	0
Local sclerosis of the sinus	9	2	5	2
Local cardiac abnormality	16	6	8	2
Systemic disease	36	19	15	2
Hypertension	16	8	6	2
Arteriosclerosis	10	3	5	2
Vegetative neurosis	8	5	3	0
Dietary deficiency	7	3	4	0
Dermatographia	5	5	0	0
Disturbance associated with the menopause	5	4	1	0
Raynaud's disease	4	4	0	0
Digitalis intoxication	4	1	3	0
Syphilis of the central nervous system	4	3	1	0
Age				
Average	45.6	41.6	50.9	69.0
Lowest	13	13	24	64
Highest	74	72	72	74

our experience, the usual cause for failure to reproduce an attack in cases in which it is suspected that syncope is due to a hyperactive carotid sinus reflex. To ascertain the location of the sinus it is advisable to extend the head. This position throws the sinus forward so that as a result it can be easily palpated. One should be certain that the carotid sinus remains under the palpating fingers during pressure and should remember that the bifurcation may be located either above or considerably below its usual position in the neck. We have observed patients in whom the sinus was situated along the lower end of the larynx rather than at its usual location along the angle of the jaw. As an attack occurs more readily when the patient is in the upright than when he is in the horizontal position, the test should be performed with him sitting or standing. Hysteroneurosis can be differentiated by infiltrating the region of the sensitive sinus with a 1 per cent solution of procaine hydrochloride. This abolishes the induced attack in patients suffering

from the true syndrome. Likewise, suggestion, occlusion of the carotid artery below the sinus and pressure over various other areas should not initiate a typical seizure.

When symptoms similar to those occurring in association with the carotid sinus syndrome are due to other causes, they cannot be reproduced by stimulation of the carotid sinus and they can be ruled out with the aid of the tests described. The carotid sinus syndrome may simulate atypical petit mal, grand mal or a narcoleptic or a cataleptic seizure, but these types of attack cannot be induced by stimulation of the carotid sinus.

It has been pointed out that the response of the carotid sinus in patients suffering from epileptic seizures is normal.[4] Similarly, we have found no relationship between the behavior of the carotid sinus reflex and postural hypotension. The relationship of carotid sinus syncope to other types of syncope has been discussed recently by Weiss.[10] His observations indicate that with rare exceptions carotid sinus syncope occurs independently of other types of syncope; that is, the hypersensitive state of this reflex is usually present without abnormality of any other mechanism responsible for fainting. Contrariwise, in other types of syncope the carotid sinus reflex is usually normal.

The type of carotid sinus reflex mechanism responsible for the symptoms in a case can be determined by observing the heart rate and the blood pressure during an induced attack and by the use of atropine sulfate and epinephrine or ephedrine. A solution of atropine sulfate given intravenously in a dose of 1 mg. (1/60 grain) abolishes the vagal reaction within three minutes but does not alter the depressor or the cerebral reaction. A subcutaneous injection of 0.5 cc. (8 minims) of a solution of epinephrine hydrochloride (1:1,000) abolishes both the vagal and the depressor reaction but does not alter the cerebral reaction. In patients having a mixed reaction it is important to determine the dominant type by the use of these drugs.

We have contrasted the behavior of patients with a hypersensitive carotid sinus with the response of normal subjects. If the patient is suffering from spontaneous manifestations of the reflex, the contrast is indeed striking. This does not imply, however, that cases in which the behavior is intermediate between normal and grossly pathologic do not occur. Such instances are frequent, but they are outside the scope of this discussion. Similarly, the intensity of the stimulus is of importance. A powerful blow to the carotid sinus results in syncope ("knock out") even when the reflex is normal.

10. Weiss, Soma: Syncope and Related Syndromes, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, London, Oxford University Press, 1935, vol. 2, chap. 8 *A*, p. 250.

TREATMENT

General Measures.—General treatment consists in correcting all associated abnormalities if possible. For elderly patients suffering from degenerative disease few beneficial measures can be taken, but for many other patients the symptoms can be lessened or relieved entirely by correcting the accompanying pathologic conditions. We have completely relieved one patient by the treatment of tuberculous glands, one by antisyphilitic therapy, two by correcting a food deficiency and four by diminishing the dose of digitalis which they were taking regularly. Whenever possible other conditions which tend to bring on an attack, such as constriction from a tight collar, fatigue, emotional upsets and worry, should be eliminated. Patients should be assured that they are not suffering from epilepsy or severe heart disease as far as the symptoms of the carotid sinus syndrome are concerned.

Specific Measures.—Vagal Type: Since the vagal type of syndrome is due to a reflex slowing or asystole of the heart, drugs which block the vagal reflex or prevent cardiac asystole in the face of a complete heart block prevent attacks. Atropine sulfate in a dose of 0.5 mg. (1/120 grain) from three to four times a day by mouth, or the equivalent of tincture of belladonna, usually prevents spontaneous symptoms. The dose should be regulated in individual cases to the smallest amount necessary to prevent symptoms, to minimize the side effects of the drug. When such effects are uncomfortable to the patient, ephedrine sulfate, 30 mg. (½ grain) three times a day, may be given by mouth instead. This drug does not prevent a reflex heart block but acts directly on the ventricles, which then assume an independent rhythm fast enough to prevent symptoms whenever the heart block occurs. The dose of ephedrine should likewise be regulated according to individual requirements. If excessive nervousness or palpitation of the heart occurs, 15 mg. (¼ grain) of phenobarbital given with each dose usually brings relief.

Surgical denervation of the carotid sinus, as described later, can be performed on patients who do not tolerate drug therapy and on those having a mixed type of syndrome in whom drugs do not give adequate relief.

Depressor Type: Since fainting in patients subject to the depressor type of syndrome is due to reflex vasodilatation through the aortic depressor nerves, atropine has no effect. A threatening attack can be aborted with epinephrine and future recurrences prevented by oral administration of 15 mg. (¼ grain) of ephedrine sulfate from three to four times a day, or by related drugs. As in cases of the vagal type, surgical denervation of the carotid sinus may be indicated.

Cerebral Type: As this type of syncope is not caused by change in the heart rate, in the blood pressure or in the cerebral blood flow, drugs which alter such functions are of no benefit. If success does not attend the correction of accompanying abnormal conditions together with an adequate application of general therapeutic measures, surgical denervation of the sinus offers the only relief. It is particularly important when the patient has attacks of such frequency and severity as seriously to disrupt his normal existence.

The operation is limited to the sensitive sinus and consists in stripping the common, internal and external carotid arteries including the bifurcation, and denuding the area of its nerve supply. A 3 inch (7.5 cm.) incision along the anterior border of the sternocleidomastoid muscle, with its center opposite the cricoid cartilage, is carried through the skin, the platysma and the superior cervical fascia to the muscle. The sternocleidomastoid muscle is then retracted laterally, exposing the upper end of the carotid sheath. The internal jugular vein is retracted medially and the common carotid artery exposed by dividing the sheath. The internal and the external carotid artery and the bifurcation are then exposed and stripped, the process being carried out from the periphery toward the bifurcation. Since the innervation may be widespread along the vessels, the arteries should be stripped for a distance of at least 2 cm. above the bifurcation. The intercarotid tissue should be freed laterally and beneath, and isolated and divided a short distance above its attachment to the bifurcation. The tissue contains many nerve fibers, and the wall of the artery at the point where these enter is thin and friable. Unless particular care is exercised, the attempt to strip this region may result in a tear in the artery.

When the intercarotid nerve is sectioned, a distinct increase in the blood pressure and the heart rate usually occurs. The changes are temporary, and the heart rate and the blood pressure return to normal within from two to six hours. None of the ten patients on whom a unilateral denervation of the carotid sinus was performed by one of us showed a permanent alteration in the blood pressure or the heart rate. Two of these patients had moderate hypertension previous to the operation, and the tension remained unchanged. We have had no opportunity to observe the effect of bilateral denervation of the carotid sinus on the blood pressure level. We have previously suggested that a permanent rise in the blood pressure in man following such a procedure is extremely unlikely. Recent experiments on animals demonstrated that the blood pressure returns to its normal level even when both carotid nerves and in addition both aortic depressor nerves are cut.[11]

11. Green, M. F., and de Groat, A.: Observations on the Late Effects of Denervation of the Carotid Sinuses and Section of the Depressor Nerves, Am. J. Physiol. **112**:488, 1935.

Results of Surgical Treatment: Ten patients subject to the cerebral type of syncope have been treated by surgical denervation of the sinus within the past two years. Two had a recurrence of symptoms, and eight remained free from attacks. Of the two patients in whom the treatment failed, one was well for three months but during the following two months had one attack of unconsciousness and frequent attacks of weakness. The other remained well for twelve months, and his subjective condition then reverted to its former state. The symptoms which returned in these two patients, however, were atypical as compared with the original symptoms, and studies have demonstrated that their recent attacks could not be duplicated by pressure over either carotid sinus.

It is interesting that these two patients had a basal metabolic rate of minus 20 and minus 25 per cent, respectively, and presented many stigmas of severe vegetative neurosis. The basal metabolic rates of the eight patients in whom the syndrome was cured, however, ranged from 0 to minus 11 per cent, and the degree of neurosis was slight. This suggests that the success of surgical treatment in patients with severe widespread neurosis associated with a low basal metabolic rate is doubtful and that such states contraindicate operative intervention.

SUMMARY

1. A hyperactive state of the carotid sinus reflex can be responsible for clinical symptoms, including attacks of syncope and convulsions.

2. Syncope and related manifestations result from one of the following three mechanisms: (*a*) cardiac slowing, (*b*) primary depression of the blood pressure or (*c*) a central reflex to the brain. The mechanism causing the reaction often appears in a mixed form.

3. Spontaneous attacks can be induced by mechanical stimulation of the carotid sinus.

4. Digitalis sensitizes the carotid sinus reflex mechanism. The routine preoperative administration of this drug, particularly to elderly patients, is not without danger.

5. Various morbid states play a rôle in sensitizing the carotid sinus reflex, and treatment of the disease, when efficacious, diminishes or abolishes the hypersensitive carotid sinus reaction.

6. Both the vagal and the depressor type of reaction can be controlled by ephedrine and epinephrine. Atropine abolishes the vagal type but has no effect on the depressor type. The cerebral type is not benefited by these drugs.

7. Surgical denervation of the carotid sinus abolishes spontaneous and induced attacks in suitable cases, but does not influence any of the unrelated accompanying symptoms.

CAROTID SINUS NERVE IN MAN

PAUL C. BUCY, M.D.
CHICAGO

In spite of extensive experimentation with animals on the carotid sinus during the past decade, little is known of the function of this mechanism in man. The following cases are reported because they presented an opportunity to study the alterations in arterial tension which result in human beings when one carotid sinus is denervated.

It is not my purpose here to review the entire literature on the subject of the carotid sinus.[1] A brief statement of the known anatomic and physiologic facts will suffice. The carotid sinus is a small bulbous enlargement of the internal carotid artery at its point of origin from the common carotid artery. It receives (in the dog) a nerve from the superior cervical sympathetic ganglion, which is always present, and a small variable nerve which may arise from the vagus (Hering[2]). Some investigators have described a small branch from the hypoglossal nerve to the carotid sinus. However, it has been shown (Code and Dingle[3]) that the carotid sinus nerve, a branch of the glossopharyngeal nerve, is the only one of these nerves concerned in the carotid sinus reflex. It is now well established that increases in pressure within the carotid sinus are associated with a fall in general arterial tension, whereas a decrease in the pressure within the sinus results in an increase in general arterial tension, a diminished flow of blood in the extremities and an increase in flow of blood and of blood pressure in the brain (Bouckaert and Heymans[4]). The effect of the carotid sinus mechanism on respiration, cardiac rate and extrasystoles is not pertinent in this connection.

Presented before the Chicago Society of Internal Medicine, Nov. 25, 1935.

From the Division of Neurology and Neurosurgery of the University of Chicago.

1. Readers are referred to Ask-Upmark,[5] Weiss and Baker[9] and Bouckaert and Heymans[4] for a more complete bibliography.

2. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927; Ueber die Wand des Sinus caroticus als Reizempfänger und den Sinusnerv als zentripetal Bahn für die Sinusreflexe, Deutsche med. Wchnschr. **51**:1140-1141, 1925.

3. Code, C. F., and Dingle, W. T.: The Carotid Sinus Nerve, Proc. Staff Meet., Mayo Clin. **10**:129-132, 1935. Code, C. F.; Dingle, W. T., and Moorhouse, V. H. K.: The Cardiovascular Carotid Sinus Reflex, Am. J. Physiol. **115**:249-260, 1936.

4. Bouckaert, J. J., and Heymans, C.: Carotid Sinus Reflexes: Influence of Central Blood-Pressure and Blood Supply on Respiratory and Vaso-Motor Centres, J. Physiol. **79**:49-66, 1933.

In addition, Bronk and Stella [5] have shown that there is a rhythmic discharge of nervous impulses over the carotid sinus nerve as long as the pressure within the sinus is above 40 mm. of mercury (in the rabbit) and that the rate of discharge is proportionate to the pressure—the higher the pressure the more rapid the discharge. The carotid sinus nerve is thus a depressor nerve which responds to pressure within the carotid sinus. The section of the carotid sinus nerve, therefore, interrupts a constant flow of depressor impulses to the vasomotor centers of the brain.

The possibility that section of one carotid sinus nerve (by section of the entire glossopharyngeal nerve) in man might give rise to some disturbance of the arterial tension was first drawn to my attention by the following case, in which the patient was operated on because of glossopharyngeal neuralgia. After the operation a marked rise in arterial tension occurred.

CASE 1.—E. P., a school teacher aged 57, was referred to the University of Chicago Clinics by Dr. L. M. Robrock, of Michigan City, Ind. She was admitted on May 3, 1935, complaining of paroxysms of sharp, stabbing pain in the left side of the throat and radiating up into the left ear. The attacks were usually precipitated by swallowing and could be brought on by touching the left tonsillar fossa. The condition was of two years' duration. She had lost 25 pounds (11.3 Kg.) during the preceding year because of her inability to eat.

Examination.—The blood pressure was 114 systolic and 72 diastolic. No abnormalities were found, except that paroxysms of pain could be elicited by touching the left tonsillar fossa.

Operation.—On May 4, 1935, with the patient under the influence of tri-bromethanol in amylene hydrate and local anesthesia, with some ether, a left unilateral suboccipital craniectomy was performed, and the left ninth cranial nerve was sectioned.

Blood Pressure.—After administration of the tri-bromethanol in amylene hydrate the blood pressure fell sharply, but it soon rose to 190 systolic and 120 diastolic (chart 1). The relationship of this hypertension to traction on the nerve or to section of it is not known. After the operation the blood pressure remained at a systolic level of 160 mm. of mercury. On the following day the arterial tension reached a peak of 174 systolic and 90 diastolic, and on the second day there occurred a peak of 190 systolic and 80 diastolic. This systolic reading was 76 mm. of mercury above the preoperative level. The tension continued to reach peaks of about 170 mm. (systolic) for several days and then subsided to a level of 130 mm. on the fourteenth postoperative day.

Spinal Fluid Pressure.—Because of the arterial hypertension lumbar puncture was made on May 4 and on May 5, but the spinal fluid pressure on the two days was only 90 and 75 mm. of fluid, respectively.

5. Bronk, D. W., and Stella, G.: Afferent Impulses in the Carotid Sinus Nerve, J. Cell. & Comp. Physiol. **1**:113-130, 1932; The Response to Steady Pressures of Single End Organs in the Isolated Carotid Sinus, Am. J. Physiol. **110**: 708-714, 1935.

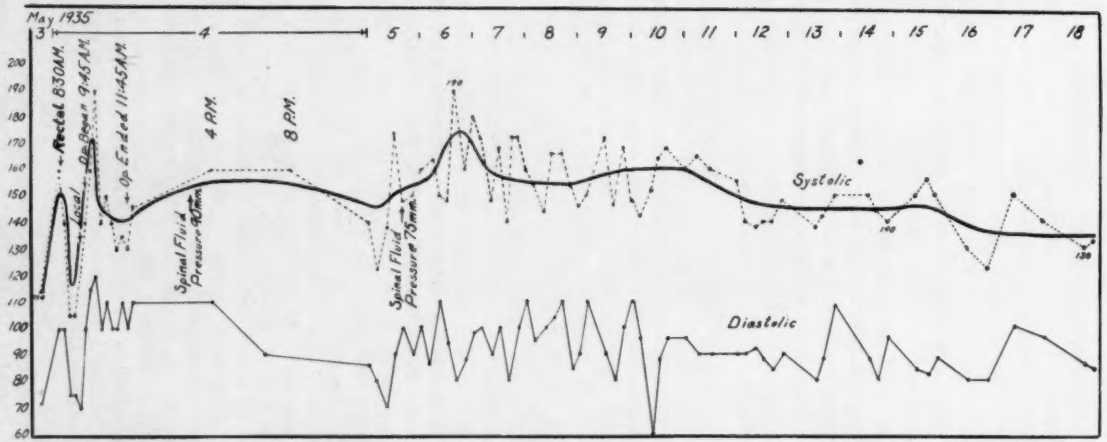

Chart 1 (case 1).—The blood pressure, systolic and diastolic, before, during and after section of the left glossopharyngeal nerve. In the upper tracing the broken line indicates the actual systolic readings; the upper solid line indicates the general trend of the systolic pressure. The lower line indicates the diastolic pressure. The changes on the day of operation, May 4, are shown in greater detail than those on the subsequent days. In this chart "rectal" indicates the time at which the injection of tri-bromethanol in amylene hydrate into the rectum was made; "local," the time when the scalp was infiltrated with a 1 per cent solution of procaine hydrochloride.

Course.—The patient had no further pain, and she was discharged on May 19, fifteen days after the operation.

Comment.—It is obvious from the normal pressure of the spinal fluid that the arterial hypertension was not the result of increased intracranial pressure. As the patient was otherwise in good health, the only cause to which the high blood pressure could be attributed was section of the ninth nerve, of which the carotid sinus nerve is a branch. If this were the case, other patients in whom the ninth nerve had been sectioned should have shown the same phenomenon. Three other such sections had been performed in the clinics. The records were reviewed, and with one exception (case 4), which will be discussed later, all the patients did show a similar postoperative arterial hypertension. The histories follow.

CASE 2.—P. C.,[6] a housewife aged 36, was referred to the University of Chicago Clinics by Dr. Loren Avery, of Chicago. She was admitted on Jan. 20, 1930. On Sept. 8, 1924, while drinking coffee, she was seized suddenly with a severe knifelike pain in the left side of the throat. She was unable to swallow, had a choking sensation and then coughed. Subsequently she suffered from similar attacks about three times a day. These were usually brought on by drinking, swallowing, opening the mouth or coughing and occasionally seemed to appear spontaneously. The pain was always severe and knifelike. It involved the pharynx, the posterior part of the tongue, the posterior nasal region and the depth of the ear, all on the left side. A week after the onset perineorrhaphy was performed, and subsequently she was free from pain for one year. The attacks then returned and became more severe and more frequent. Various medications, eradication of foci of infection (?), injection of alcohol into the trigeminal nerve, intravenous injections and chiropractic treatments were tried without relief.

Examination.—The results of examination were entirely negative except for slight hypesthesia of the lower part of the left side of the face, which was probably the result of the injection of alcohol into the fifth nerve. The blood pressure was 100 systolic and 64 diastolic.

Operation and Course.—On Jan. 23, 1930, with the patient under ether anesthesia, a unilateral left suboccipital exposure was made. The left glossopharyngeal nerve was exposed and severed.

In the midst of the operation the systolic blood pressure suddenly rose from 95 to 115 mm. of mercury (chart 2). This was at about the time the nerve was interrupted, but the exact time relationship is unknown. At the close of the operation the blood pressure rose to 140 systolic and 80 diastolic.

At 6 and at 8 p. m. on January 24 the patient seemed in good condition. At 10 p. m. she was semicomatose; the blood pressure was 150 systolic and 80 diastolic. Respiration of the Cheyne-Stokes type soon appeared. She was taken to the operating room; the wound was explored, and an extradural blood clot was evacuated. She responded immediately and made an uneventful recovery, being discharged on February 8, sixteen days after the operation. At the time of writing she has suffered from no recurrence of the pain since the operation.

6. Previously reported by Percival Bailey (Neuralgias of the Cranial Nerves, S. Clin. North America **2**:61-77, 1931).

Blood Pressure.—The systolic pressure before and during the first half of the operation ranged between 95 and 100 mm. of mercury. After a sudden rise in the midst of the operation the blood pressure remained considerably above the preoperative level, reaching as high as 148 systolic and 92 diastolic on the fourth postoperative day (not counting the peak caused by the hematoma), and returned to a systolic pressure of 110 only on the seventh postoperative day.

Comment.—The condition in this case was complicated by the occurrence of a postoperative extradural hematoma which resulted in a sharp elevation in the arterial tension on the evening of the first postoperative day. However, this hemorrhage could not have explained the sharp rise in pressure during and immediately after the operation, and it is unlikely that it had anything to do with the prolonged hypertension which continued for a week after the operation, especially as the hematoma was evacuated and the patient showed no further signs of increased intracranial pressure or of medullary compression.

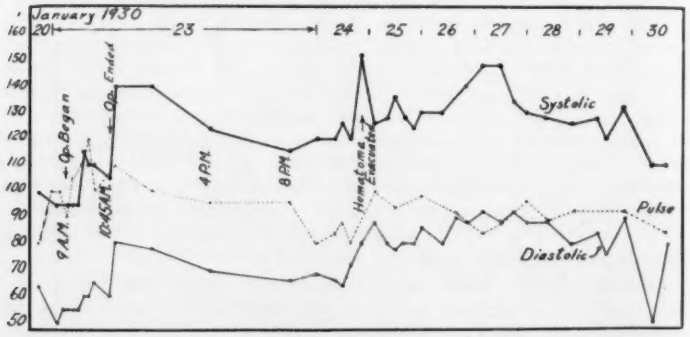

Chart 2 (case 2).—The systolic and diastolic blood pressures and pulse rate, before, during and after section of the left ninth cranial nerve. Ether anesthesia.

CASE 3.—E. O., a housewife aged 65, was referred to the University of Chicago Clinics by Dr. T. S. F. Johnson, of Joliet, Ill. She was first admitted on Sept. 8, 1934, complaining of paroxysms of severe pain in the right side of the face, involving all three divisions of the trigeminal nerve, particularly the ophthalmic and the maxillary. This pain had been present for fifteen years and was growing more severe.

Examination.—No abnormality was revealed other than the attacks of severe pain which were precipitated by talking or by touching the right cheek. The blood pressure was 160 systolic, 90 diastolic.

Operation and Course.—The first operation was performed on Sept. 11, 1934, with the patient under ether anesthesia. The posterior root of the right trigeminal nerve was sectioned. The approach was through the temporal fossa.

The blood pressure dropped to 110 mm. of mercury, systolic, during the operation but subsequently varied little from the preoperative level (chart 3).

After the operation the patient was completely relieved from her pain and was discharged on September 19, eight days after the operation.

Second Admission.—On Nov. 22, 1934, the patient again entered the clinics. About the middle of October she had begun to have a feeling as though something were stuck in the region of the left tonsil, but she had no pain until November 1, when she was suddenly seized with a paroxysm of severe pain in the left side of the throat. The attacks had recurred as frequently as ten to twelve times an hour from that time on. The pain was confined to the left side of the throat and the tonsillar region, never radiating to the ear. It was usually precipitated by swallowing.

Examination.—The blood pressure was 155 systolic and 90 diastolic. Except for total anesthesia in the distribution of the right fifth nerve there were no abnormalities.

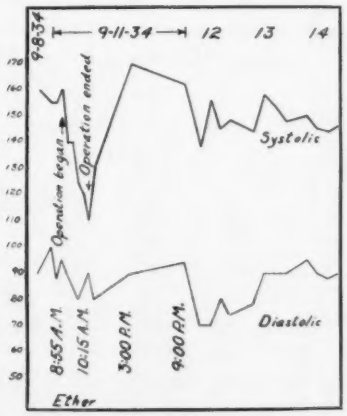

Chart 3 (case 3).—The blood pressure before, during and after section of the right trigeminal nerve by the temporal approach.

Operation.—The second operation was performed on Nov. 24, 1934, with the patient under the influence of tri-bromethanol in amylene hydrate (90 mg. per kilogram of body weight) and local anesthesia. The cerebellum was elevated, and the left ninth cranial nerve was sectioned.

Blood Pressure.—A precipitous drop occurred after the administration of the anesthetic, but the blood pressure shortly returned to the preoperative level. After the operation it rose to 190 systolic and 110 diastolic, and on the third postoperative day it reached 200 systolic and 110 diastolic. It returned to the preoperative level about six days after the operation (chart 4).

Lumbar Punctures.—On the first and the second postoperative days (November 25 and 26) lumbar puncture was made because of the arterial hypertension. The spinal fluid pressure on the two days was 160 and 165 mm. of fluid, respectively.

The patient was discharged on Dec. 3, 1934, eleven days after the operation and has had no further pain at the time of writing.

Comment.—This case is particularly interesting because of the association of trigeminal and glossopharyngeal neuralgia, an association which Peet [7] has found to occur frequently. As the trigeminal neuralgia was on the right and the glossopharyngeal neuralgia was on the left, there can be no question of the accuracy of the diagnoses. The absence of any rise in the arterial tension after the section of the fifth nerve as compared with the marked rise after the ninth nerve was sectioned leaves little reason to doubt that the arterial hypertension was the result of the interruption of the carotid sinus nerve.

CASE 4.—A. W., a man aged 39, was admitted on Aug. 13, 1930, complaining of extreme dizziness, nausea, vomiting, headache, pain in the throat and ear on the left side, pain and swelling in front of the left ear, weakness of the left side of the face and impaired hearing in the left ear.

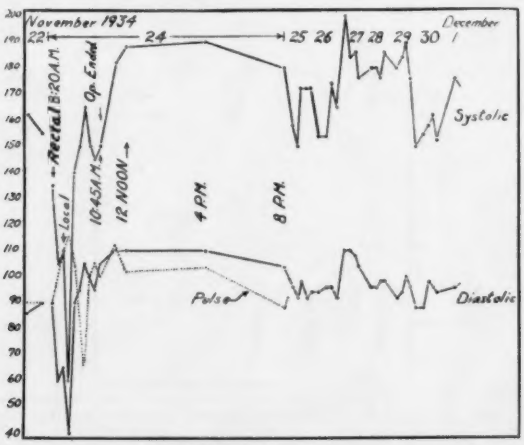

Chart 4 (case 3).—The blood pressure before, during and after section of the left glossopharyngeal nerve. In this chart "rectal" indicates the time at which the injection of tri-bromethanol in amylene hydrate into the rectum was made; "local," the time when the scalp was infiltrated with a 1 per cent solution of procaine hydrochloride.

The patient had first noted the swelling near the left ear in October 1929. It had gradually increased in size. The other symptoms had appeared in the course of the two months preceding admission.

Examination.—A swollen indurated area was present below and in front of the left ear. There were paralysis of the left side of the face, partial deafness of the left ear of the middle ear type, hyperesthesia in the depth of the left external auditory meatus and hypesthesia in the area of distribution of the second and third cervical nerves on the left side.

7. Peet, M. M.: Glossopharyngeal Neuralgia, Ann. Surg. **101**:256-268, 1935.

A diagnosis of malignant neoplasm of the left side of the neck, with the involvement of various cranial and cervical nerves, was made. Section of the ninth cranial nerve was suggested, but the patient refused operation.

Second Admission.—The patient was readmitted to the hospital on Sept. 9, 1930. The mass in the left side of the neck had increased in size, and the pain, chiefly deep in the left ear and also in the left side of the throat, had increased greatly in severity. He also complained constantly of dizziness.

Examination revealed no change except an increase in the size of the tumor.

Operation.—On Sept. 17, 1930, operation was performed with the area under local anesthesia. Through a unilateral suboccipital exposure the cerebellum was retracted medially, and the seventh, eighth and ninth cranial nerves on the left side were sectioned. The patient still complained of pain in the base of the tongue, and pain in that region could be elicited by touching the tenth nerve. The uppermost fibers of the tenth nerve were then sectioned. After the operation he was hoarse and for a time was unable to swallow. Some pain in the neck persisted.

Blood Pressure.—The blood pressure fluctuated considerably during the operation. It was followed for two days only, but no elevation from the preoperative level was observed during that time (chart 5).

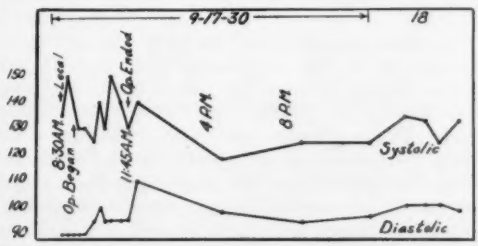

Chart 5 (case 4).—The blood pressure during and after section of the left seventh, eighth, ninth and part of the tenth cranial nerves.

Comment.—This was the only one of the four cases in which the ninth cranial nerve was sectioned in which a postoperative rise in blood pressure did not occur. It is believed that in this case the tumor had probably invaded and destroyed the carotid sinus nerve prior to the operation.

After having this phenomenon drawn to my attention by case 1 and its occurrence confirmed by cases 2 and 3, I was fortunate in having the opportunity to section the ninth nerve on the right side (all the previous ones had been on the left side) in a patient suffering from glossopharyngeal neuralgia. More careful observations during the operation were possible in this instance than in the preceding cases.

Case 5.—N. L., a clerk 40 years of age, was first seen in the neurologic outpatient department of the University of Chicago Clinics on Feb. 17, 1934. He complained of paroxysmal attacks of pain in the posterior part of the tongue and in the throat, which were brought on by swallowing and by talking. The pain did

not radiate into the ear. He stated that he also had a dull, more continuous pain in the right temple and at times in the right side of the face. The pain was always absent during the summer months. Because of the atypical nature of the condition he was kept under observation for a time.

The patient returned on Oct. 23, 1935. The pain had not been relieved during the summer, and he had decided to have the operation. In order to confirm the diagnosis Dr. J. R. Lindsay anesthetized the throat with cocaine. This completely relieved the pain.

Examination.—The general physical and neurologic examinations gave negative results. The blood pressure was repeatedly determined on both arms and was found to vary between 108 systolic and 65 diastolic and 112 systolic and 65 diastolic.

The diagnosis was glossopharyngeal neuralgia on the right side.

Operation.—On Nov. 2, 1935, with the patient under ether anesthesia, a suboccipital exposure was made on the right side; the cerebellar hemisphere was elevated, and the glossopharyngeal nerve was severed.

The patient made an uneventful recovery and was discharged a week later, on Nov. 9, 1935.

Blood Pressure.—During the first part of the operation, while the exposure was being made, the blood pressure varied between 90 and 120 mm. of mercury systolic, and between 50 and 75 mm. diastolic. During this period the blood pressure was determined at five minute intervals. After the nerve was cut, it was determined at one minute intervals. At the time of sectioning of the nerve the systolic pressure fell slightly, and the diastolic pressure fell from 60 to 40 mm. Shortly thereafter the blood pressure began to rise steadily, and in seven minutes it reached a peak of 186 mm. systolic and 80 mm. diastolic (chart 6 *B*). It then fell to the preoperative level only to rise to a second peak of 162 systolic and 72 diastolic and then subside to 106 systolic and 58 diastolic at the close of the operation. Very soon after the operation it rose again and continued between 130 and 145 systolic and between 72 and 100 diastolic for the remainder of the patient's stay in the hospital. When he was seen on Nov. 13, 1935, eleven days after the operation, the blood pressure was 132 systolic and 70 diastolic (chart 6 *A*).

Cardiac and Respiratory Rate.—It was not feasible to determine these as frequently during the operation as the blood pressure was measured. However, the observations which were made indicated a rise in both the cardiac and the respiratory rate immediately after the nerve was severed. During the following days the respiratory rate remained normal, and nothing definite could be stated concerning the cardiac rate. The pulse was definitely more rapid, but this may have had no significance, as the patient ran a slight febrile course.

This case is particularly interesting in that it shows the immediate marked rise in systolic blood pressure which occurs soon after the glossopharyngeal nerve is severed and the secondary rise which appears several hours later and is most marked on the second or third postoperative day. It is to be anticipated that the blood pressure in this case, as in the others, will soon return to normal, although a sufficiently long period of observation has not occurred at the time of writing to determine this point.

Although the absence of any rise in blood pressure after section of the fifth nerve in case 3 offered a fair control of these observations, it

was thought advisable to review another group of cases in which the surgical approach was much the same as that for glossopharyngeal neuralgia but in which the ninth nerve was not disturbed. Reports follow of two cases typical of this group.

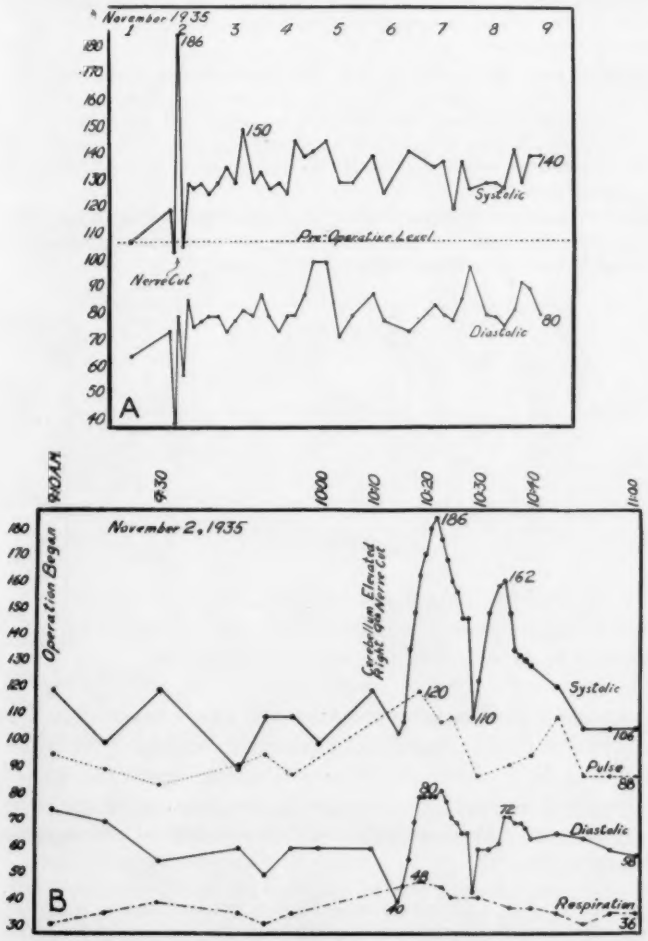

Chart 6 (case 5).—*A*, the elevation in blood pressure resulting from section of the right glossopharyngeal nerve. *B*, a more detailed graph of blood pressure, pulse and respiration during the operation. Determinations were made by Dr. Harold Koch. Ether anesthesia.

CASE 6.—L. R.,[6] a carpenter aged 59, was referred to the University of Chicago Clinics by Dr. George B. Hassin, of Chicago. He had suffered for twelve years

from typical trigeminal neuralgia, which involved the entire right side of the face. Because of a gross anatomic anomaly of the floor of the temporal fossa, previous operations had been confined to section of the peripheral divisions of the nerve and had given only temporary relief. A section of the fifth nerve by the suboccipital approach (Dandy) was therefore decided on.

Examination.—No abnormalities were revealed except an absence of sensation over the greater part of the face on the right side. The blood pressure was 140 systolic and 50 diastolic.

Operation and Course.—On March 7, 1930, operation was performed with the patient under ether anesthesia. Unilateral suboccipital incision and craniectomy were done. The cerebellum was retracted medially until the fifth nerve was exposed. It was divided by a hooked knife, and the wound was closed.

The postoperative course was uneventful, and the patient was discharged twelve days after the operation.

Blood Pressure.—Variations in blood pressure during the operation were not unusual. The blood pressure was followed for two days after the operation and was found to remain at the preoperative level (chart 7).

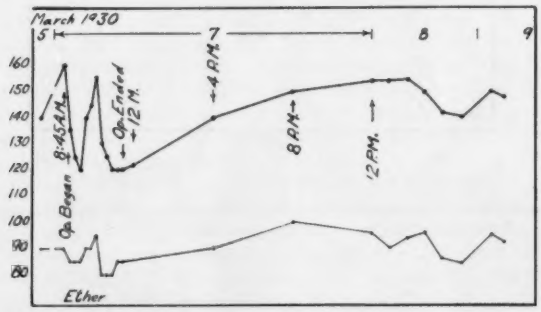

Chart 7 (case 6).—The effect on the blood pressure of section of the right fifth cranial nerve by the suboccipital approach. Ether anesthesia.

Comment.—The operative procedure necessary to expose and section the fifth nerve by the suboccipital approach differs little from that used in sectioning the ninth nerve. This case illustrates clearly that the operative procedure necessary for exposure of the nerve is not the cause of the hypertension and leaves little doubt that section of the ninth nerve is directly responsible.

CASE 7.—E. N.,[6] a housewife aged 65, was referred to the University of Chicago Clinics by Dr. Peter Bassoe, of Chicago, and was admitted on Dec. 13, 1929. She had suffered from paroxysms of pain in the left side of the face for eighteen years. Seven years previously a partial retrogasserian neurectomy had been performed at another hospital, with only temporary relief. Two years later the wound was reexplored, and the section of the nerve was completed. Again the pain was relieved for a short time.

Examination.—Enophthalmos on the left and ptosis of the left upper eyelid were noted. The left pupil did not react to light. Ocular movements were normal. There was partial weakness of the left side of the face.

The blood pressure was 215 systolic and 95 diastolic. The heart was enlarged, and occasional extrasystoles were present. The patient gave a history of occasional attacks of precordial pain. There was a moderate degree of peripheral arteriosclerosis.

The patient was placed under the care of a cardiologist for a time.

Operation and Course.—On March 18, 1930, operation was performed with the patient under ether anesthesia. The blood pressure was 180 systolic and 85 diastolic. The usual unilateral suboccipital exposure was made. The cerebellum was retracted medially, and a small meningioma was removed from the left side of the pons.

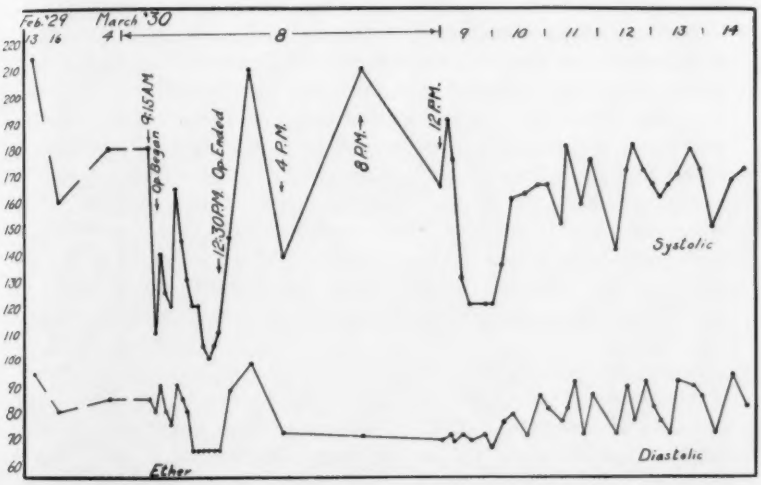

Chart 8 (case 7).—The blood pressure as affected by the removal of a small meningioma from the right side of the pons by a suboccipital approach. Ether anesthesia.

After the operation the patient was completely relieved of pain and remained so. The weakness of the left side of the face was more marked for a time, and a corneal ulcer developed, which soon healed.

Blood Pressure.—During the operation the blood pressure was considerably below the preoperative level (chart 8). After the operation, except for two occasions during the afternoon of the day of operation when the systolic pressure reached 210 and one on the following morning when it reached 190, the blood pressure remained at or below the preoperative level of 180.

Comment.—The condition was complicated by cardiovascular disease, but the results in this case as well as those in case 6 show that the sub-

occipital approach to the nerves in the posterior cranial fossa is not responsible for the postoperative hypertension observed after section of the ninth cranial nerve.

REVIEW OF THE LITERATURE

An extensive review of the literature dealing with glossopharyngeal neuralgia reveals no observations on the blood pressure after section of the glossopharyngeal nerve, with the exception of those in the cases briefly mentioned in the excellent monograph by Ask-Upmark.[8] In the first of these cases a sharp rise of arterial tension (systolic), of from 100 to 175 mm. of mercury, occurred when the right ninth cranial nerve was cut; in the second a momentary drop in blood pressure occurred, and in the third a temporary but sharp rise was noted. In no instance were prolonged observations made. Weiss and Baker[9] reported one case (possibly the same as Ask-Upmark's case 1) in which section of the right glossopharyngeal nerve intracranially was followed by an immediate sharp rise in arterial tension. They reported another interesting case in which a patient suffering from fainting attacks was found to have a tumor of the right carotid sinus. Pressure on the tumor reproduced the attacks. The patient was operated on; the tumor was removed, and the carotid sinus was denervated. There occurred an immediate sharp rise in the blood pressure, which increased to a peak of 225 systolic and 120 diastolic from a preoperative pressure of 160 systolic and 100 diastolic. The increase in the arterial tension persisted for thirty-six hours after the operation. Budde[10] reported a case in which section of the nerve of the sinus resulted in an immediate moderate rise in blood pressure. Leriche, Fontaine and Froehlich[11] reported seven instances of denervation of the carotid sinus. Both sinuses were denervated in five cases and one in two cases. Immediately after denervation they noted a marked rise in arterial tension, which subsided in a few days, the tension becoming normal. No effect on the cardiac rhythm or the respiratory rate was observed.

Bevan and McCarthy[12] in reporting a case of tumor of the carotid body and reviewing the reports of 142 other cases referred to reports

8. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation: Anatomical, Experimental and Clinical Investigation, Including Some Observations on the Rete Mirabile Caroticum, Acta psychiat. et neurol., supp. 6, 1935, pp. 1-374.

9. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflexes in Health and Disease, Medicine **12**:297-354, 1933.

10. Budde, M.: Chirurgische Erfahrungen über den Carotissinusdruckversuch, Ztschr. f. d. ges. exper. Med. **50**:207-211, 1926.

11. Leriche, R.; Fontaine, R., and Froehlich, F.: L'énervation sinu-carotidienne, Presse méd. **43**:1217-1220, 1935.

12. Bevan, A. D., and McCarthy, E. R.: Tumors of the Carotid Body, Surg., Gynec. & Obst. **49**:764-779, 1929.

of fainting attacks and attacks of "Stokes-Adams syndrome" precipitated by pressure on the tumor but made no mention of alterations in blood pressure in association either with the tumor or with operation on it. Rankin and Wellbrock [13] in another report of such tumors referred to attacks of fainting elicited by pressure on the tumor but made no reference to arterial tension.

Dorrance,[14] discussing ligation of the vessels of the neck, stated that ligation of the common carotid artery results in a reduction of the pressure in the carotid sinus and that this in turn may result in extrasystoles and even fibrillation. He made no reference to any rise in blood pressure caused by this procedure.

Except for the fact that pressure over the carotid sinus will induce a fall in blood pressure and a slowing of the cardiac rate (see Weiss and Baker [9] for a fuller discussion) few observations have been made concerning the carotid sinus mechanism in man.

COMMENT

In view of the changes in blood pressure observed in the cases reported here and in the few instances cited from the literature, there can be little doubt that the section of one carotid sinus nerve or of one glossopharyngeal nerve results in a temporary rise in arterial tension. That the rise is only temporary, persisting for from five to twelve days in our cases, is not surprising, since several investigators (Green, De Groat and McDonald,[15] Green and De Groat,[16] Koch and Mattonet [17] and others) have found experimentally that even after section of both carotid sinus nerves and of both aortic depressor nerves the resultant rise in blood pressure is not permanent; at least it is not maintained nearly at the initial high level.

The explanation of the hypertension which ensues after section of a carotid sinus nerve seems simple. Bronk and Stella [5] demonstrated a constant flow of nervous impulses over the carotid sinus nerve. Their

13. Rankin, F. W., and Wellbrock, W. L. A.: Tumors of the Carotid Body, Ann. Surg. **93**:801-810, 1931.

14. Dorrance, G. M.: Ligation of the Great Vessels of the Neck, Ann. Surg. **99**:721-742, 1934.

15. Green, M. F.; De Groat, A. F., and McDonald, C. H.: Observations on Denervation of the Carotid Sinus and Section of the Depressor Nerves as a Method of Producing Arterial Hypertension, Am. J. Physiol. **110**:513-520, 1935.

16. Green, M. F., and De Groat, A. F.: Observations on the Late Effects of Denervation of the Carotid Sinuses and Section of Depressor Nerves, Am. J. Physiol. **112**:488-492, 1935.

17. Koch, E., and Mattonet, K.: Versuche zur Frage der arteriellen Hypertonie nach Dauerausschaltung von pressoreceptorischen Kreislaufnerven, Ztschr. f. d. ges. exper. Med. **94**:105-113, 1934.

rate is proportionate to the pressure within the sinus. These impulses have a depressor action. When they are abolished, the pressure rises as a result. The rise, however, is temporary because the other cardiovascular regulatory mechanisms soon gain control.

It would appear from these cases that section of either the right or the left carotid sinus nerve will give the same results in man. In these cases no significant changes in pulse rate or respiratory rate were observed unless it was in case 5 immediately after the section of the nerve.

SUMMARY

Four cases of glossopharyngeal neuralgia treated by intracranial section of the glossopharyngeal nerve are reported. In each instance a marked rise in blood pressure occurred after the operation and lasted several days. This is interpreted as due to interruption of the carotid sinus nerve, a branch of the glossopharyngeal nerve.

A case in which a malignant neoplasm of the neck was treated by intracranial section of the seventh, eighth, ninth and part of the tenth cranial nerves is reported; no rise in blood pressure occurred, probably because of involvement of the carotid sinus nerve by the tumor.

Two cases are reported in which a similar surgical approach was used, but the ninth cranial nerve was not sectioned. No rise in blood pressure occurred.

The very limited pertinent literature is reviewed.

The conclusion is drawn that in man the section of one carotid sinus nerve or of the glossopharyngeal nerve of which it is a branch results in a rise in arterial tension of a few days' duration.

ADRENAL SYMPATHETIC SYNDROME WITH UNUSUAL VARIATIONS IN CARDIAC RHYTHM

REPORT OF A CASE

ALEX M. BURGESS, M.D.

GEORGE W. WATERMAN, M.D.

AND

F. B. CUTTS, M.D.

PROVIDENCE, R. I.

Within the last few years a great deal of attention has been given to the relation of the adrenal glands to arterial hypertension. Both hyperplasia and tumor of these organs have been found in some instances to be associated with high blood pressure. In particular, a small number of instances of tumor arising from the chromaffin tissue of the adrenal medulla have been reported as characterized by an unusual clinical picture, the most striking feature of which is paroxysmal hypertension. It is the purpose of this communication to report an instance of this condition, including certain observations on the heart which are of interest.

Among the published reports of instances of this type of adrenal tumor there have been several excellent descriptions of the associated clinical picture, of which condition our patient presented an extreme example. This symptom complex has been called the "suprarenal sympathetic syndrome" by Belt and Powell [1] "in contradistinction," as they put it, "to the 'suprarenal genital syndrome' which is associated with certain neoplasms of the cortical portions of these glands." It is characterized by paroxysmal attacks of hypertension, with tachycardia, pallor and nausea and at times vomiting and by a feeling of great tension, often with cyanosis and choking and sometimes with pulmonary edema. These authors have recently published, with the report of a complete study of a typical case, an excellent survey of the literature, including a review of twenty-three reported cases in which the clinical manifestations may be considered definitely as characteristic of the condition.

At about the same time Coller, Field and Durant [2] reported a striking case of a youth of 16 in which operation was followed by an apparently

1. Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, Surg., Gynec. & Obst. **59**:9 (July) 1934.

2. Coller, F. A.; Field, H., Jr., and Durant, T. M.: Chromaffin Cell Tumor Causing Paroxysmal Hypertension, Relieved by Operation, Arch. Surg. **28**:1136 (June) 1934.

complete recovery. To these may be added the recent description of three additional instances of the condition by Pincoffs,[3] in one of which the tumor was found in the median line, apparently arising from a chromaffin cell rest in a prevertebral sympathetic ganglion. Such rests of pheochromocytes are known to occur normally in these ganglions, and tumors arising from them have been given the name paraganglioma, which, in our opinion, is an undesirable term, as it is based merely on the location of the tumors, whereas the term pheochromocytoma indicates the type of cell and should, we believe, be applied to these neoplasms, whether they arise from the medulla of the adrenal glands or from rests of chromaffin cells elsewhere.

REPORT OF CASE

R. N., a 25 year old Jewish housewife, consulted one of us on April 20, 1933. At that time she complained of attacks of palpitation, which she described as "thumping" in the chest. They occurred usually during the night and began two years before examination, after the sudden death of her father. The attacks lasted five or ten minutes and were associated with pallor and gagging but no vomiting. There was never loss of consciousness. As a rule the attacks awakened the patient in the night, but occasionally one occurred during the day. She stated that they made her throat "expand and the vessels stand out" and that although the action of the heart was forceful and uncomfortable, the rate was not accelerated. There had been no dyspnea on exertion. The patient had consulted many doctors without relief. Rentgenologic study of the gastro-intestinal tract suggested appendicitis, but appendectomy performed in April 1932 was not followed by any improvement. Tonsillectomy was performed in May 1932.

History.—A brief summary of the relevant facts reported in the record shows that the patient had measles, pertussis and scarlet fever in childhood. At the age of 6 years she had pneumonia followed by empyema, which was drained. Menstruation began at the age of 14 and always occurred from six days to three weeks late. She usually had flow for two days and sufficient discharge to stain a napkin for four days and had occasional cramps. A review of the function of the various systems gave essentially negative results, except that a constant tendency to constipation was noted. Her average weight was 105 pounds (47.5 Kg.), and she said she had lost 5 pounds (2.3 Kg.) during the previous five weeks.

Marital and Family History.—The patient had been married a year and a half, and no pregnancy had occurred. The family history was negative as regards benign or malignant tumor or other diseases relevant to her problem. In particular, there was no record of attacks similar to hers.

Physical Examination and Course.—The patient was 61½ inches (159.2 cm.) tall (with shoes) and weighed 101½ pounds (46.03 Kg.) clothed. The temperature was 98.3 F. and the pulse rate was 72. The blood pressure was 118 systolic and 76 diastolic.

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3. Pincoffs, M. C.: Medullary Tumors of the Adrenal Glands, read at the nineteenth annual clinical session of the American College of Physicians, Philadelphia, April 30, 1935, to be published.

The physical examination in general gave negative results. The heart was apparently not enlarged; its rate and rhythm were normal, and no murmurs were heard. The reaction to exercise was considered normal. The urine was normal. A summary of the facts elicited in the examination at that time led to a tentative diagnosis of cardiac neurosis, although it was noted that the attacks were unusual and their origin obscure. The patient was advised to report attacks promptly in the hope that one might be observed, and she was placed temporarily on a regimen of partial rest and advised to take phenobarbital, ¼ grain (0.0162 Gm.) three times daily and ½ grain (0.0324 Gm.) at bedtime. It was suggsted that she see a neuropsychiatrist.

A report from Dr. Kramer showed the basal metabolic rate to have been —14.6 per cent a few weeks before the examination.

The patient was seen again on May 15 and on June 8. On the latter date she had just recovered from an attack which occurred while she was shopping, but nothing abnormal could be found. The color was good; the heart was apparently normal, and the blood pressure was 104 systolic and 70 diastolic.

After that the patient did not report further and consulted other physicians, both in Providence and in New York. Finally, as had been suggested to her, she called on a neuropsychiatrist, Dr. Charles A. McDonald. He elicited the same history as to attacks, except that at that time she stated that they usually lasted twenty minutes and were at times associated with headache of a "binding" nature. He wrote as follows: "I saw her several times until she became pregnant, and on Oct. 27, 1934, when she told me about her pregnancy she said that since becoming pregnant she had stopped vomiting, retching and expectorating. The next and last time I saw her was on Jan. 22, 1935. She was in the hospital suffering from what I then called a vasovagal spell, and I noted that the attack was like the type she had had before, but much worse."

The patient was next seen, by another of us, on Oct. 25, 1934, having been referred by Dr. McDonald for care of her pregnancy. Her last menstrual period had occurred on Sept. 1, 1934. The history obtained at that time was similar to that elicited before, except that after the onset of pregnancy the attacks had diminished greatly in frequency and severity and had been practically absent for four weeks. The result of physical examination in general was essentially as noted before.

The weight (clothed) was 104¾ pounds (47.51 Kg.); the blood pressure, 115 systolic and 70 diastolic and the pulse rate, 72. The urine was normal.

On Nov. 23, 1934, the patient reported several attacks of palpitation, nausea and vomiting, such as she had had before she became pregnant. The blood pressure was 120 systolic and 80 diastolic. The weight was 106¾ pounds (47.96 Kg.). The urine was normal.

On Dec. 18, 1934, the blood pressure was 120 systolic and 80 diastolic. The weight was 108¼ pounds (49.1 Kg.). The patient stated that she felt very well as far as her pregnancy was concerned but that she still had attacks as before, not relieved by vomiting. Her general condition seemed excellent.

On Jan. 18, 1935, the patient said that she was not so nauseated as previously and distinguished between what she called her "pregnancy nausea," which was "easy" and did not trouble her in the least, and her "old" nausea, which was accompanied by gagging, palpitation and headache. She also complained that she felt a lump in her abdomen, which became very hard when an attack occurred. Examination showed nothing unusual except a pregnant uterus. No other mass was found. Urinalysis gave negative results.

The following is quoted from the office record of Jan. 21, 1935: "The patient's sister called by telephone this afternoon at 3:00 to say that Mrs. N. had been vomiting all day, was most distressed and was vomiting blood. On my arrival, as I walked into her room, she was leaning over the edge of her bed, her skin was dusky bluish gray, and frothy pink serum was coming out of her mouth into a basin on the floor. She was coughing and gagging. Her pulse rate was about 144, and the beat was regular. The paroxysm lasted about two minutes after my arrival, and then she sank back exhausted. Her color gradually became better, and her strength returned. Suddenly she looked very anxious and said 'Now it's coming again,' and put her hand to her precordium. I listened, and her heart had taken on a strong, full, irregular beat, the rate being about 50 but with extrasystoles, or skipped beats. She complained of severe binding headache and then of a lump rising in her abdomen, which examination showed to be the uterus, which contracted and raised itself as if in the second stage of labor, except that there was no pain or bearing down. After that she became faint, and severe nausea, vomiting and gagging occurred. She was very cyanotic, and as I listened over the precordium, the cardiac rhythm changed, becoming rapid and regular. At the same time moist râles appeared, and bloody frothy serum typical of pulmonary edema was coughed or vomited. Gradually the violence of the attack subsided, and the patient sank back exhausted. Episodes such as have been described occurred every three to five minutes. She was transferred to a hospital, where sedatives (morphine and chloral hydrate) seemed to quiet her, and the attacks stopped. She stayed in the hospital for one week. As she had no more attacks she was allowed to go home, the pulse rate and the blood pressure being normal. For several days after her admission to the hospital her pulse was rapid and there were moist râles in the chest and a murmur over the first and second left interspaces near the sternum."

On Feb. 12, 1935, the report in the office record was: "The patient had a similar series of episodes at home today, eventually controlled by morphine, scopolamine and atropine, although it seemed as if she was going to die of pulmonary edema in one attack."

When the patient was seen in the office on Feb. 22, 1935, she seemed normal in every way. The weight was 114¾ pounds (52 Kg.). When she was seen on March 4, 1935, she was having a slight attack. In this attack, as in others observed later, there were cyanosis, pallor, marked uterine contraction, nausea and vomiting. The attacks continued with intervals of several days' freedom up to the time of her delivery on March 29. The child was premature and died after several hours.

Treatment of various sorts were tried—ordinary sedatives (pentobarbital, morphine and scopolamine), epinephrine, atropine and quinidine—without definite effect. It is worthy of note that at the time of delivery the patient did not suffer from an attack, although such attacks did occur about twenty-four hours later. Figure 1 illustrates the changes in blood pressure noted in an attack on March 30.

As the attacks varied greatly in their intensity and frequency, it is perhaps best to describe a typical and severe example, such as occurred on April 6. When seen the patient showed a heart rate of from 120 to 140, with a regular rhythm and a loud systolic murmur audible to the left of the sternum in the second and third spaces. The color was good, and she was relaxed and drowsy. The blood pressure was 65 systolic and 40 diastolic. After a few minutes the systolic pressure was noted to be 100, and the sounds were distinctly louder, increasing in loudness during the next ten or twelve beats in a striking crescendo. As the sounds became very loud, the rate became slower, and then distinctly irregular.

The blood pressure at that time was 240 systolic and 180 diastolic. After a few seconds the rhythm again became regular, and a gallop rhythm developed. Absence of the systolic murmur was noted. Repeated observations of blood pressure showed a gradual fall during the next ten minutes, with a disappearance of the gallop rhythm and a reappearance of the murmur when the systolic pressure reached about 120. The fall in pressure continued until the original level, approximately 60 systolic and 45 diastolic, had been reached. This whole cycle was repeated every fifteen minutes throughout the early part of the day. Later the intervals between attacks became much longer. With the onset of the slow strong beats and the rise in pressure, the patient became pallid and then cyanotic and complained of fulness in the head and the throat and then of nausea. She vomited in many of the attacks and in some coughed up a pinkish, frothy fluid and showed moist râles in the lungs. The severity of the attacks was mitigated somewhat by sedatives. Electrocardiographic studies were made throughout the entire cycle

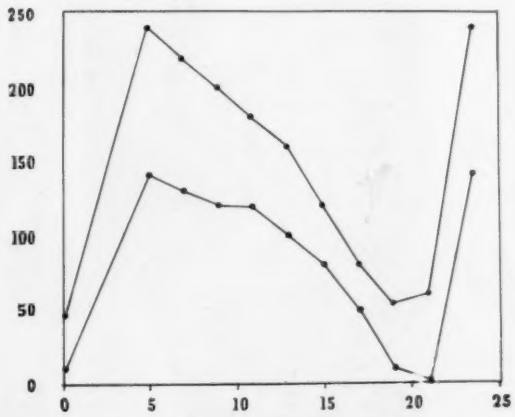

Fig. 1.—Serial observations of blood pressure during an attack on March 30. The upper line indicates systolic pressures, the lower line, diastolic pressures, in millimeters of mercury. Time is given in minutes.

and were correlated with symptoms and with changes of blood pressure. These are discussed later in this paper.

As the patient's puerperium was otherwise normal, she was removed on the tenth day post partum to the Jane Brown Memorial Hospital. Retrograde pyelograms showed a marked displacement downward and compression of the upper part of the right kidney, and a tentative diagnosis of pheochromocytoma of the right adrenal gland was made.

Roentgen treatment was carried out by Dr. Batchelder, eleven treatments being given, but by May 6 recurrent attacks with pulmonary edema had become so alarming that operation was decided on.

Laboratory studies on March 8, 1935, showed the dextrose content of blood to be 125 mg. per hundred cubic centimeters (fasting), the nonprotein nitrogen content 31 mg. and the carbon dioxide-combining power 53 volumes per cent. On March 25, 1935, the dextrose content of the blood was 110 mg. per hundred cubic

centimeters (fasting), and nonprotein nitrogen 29 mg. Slight glycosuria was observed thereafter on several occasions. The Wassermann reaction of the blood was negative.

Operation.—On May 8, 1935, operation, requiring one hour, was performed, with the patient under preliminary anesthesia with phenobarbital and morphine sulfate and later nitrous oxide with oxygen. Technic: An upper right rectus incision was made. When the peritoneum was opened, the liver was found pushed down below the level of the umbilicus by a tumor of the adrenal gland, which was about 10 cm. in diameter. To give better exposure beneath the surface of the liver, a horizontal incision was made from about the midpoint of the longitudinal incision, opening the flank to the midaxillary line. The liver was then reflected, and the tumor was exposed retroperitoneally and above the kidney. The peritoneum

Fig. 2.—Pyelogram showing displacement of the right kidney downward and outward.

was incised longitudinally, and the tumor was shelled out, a definite line of cleavage being established. The tumor was removed without difficulty and with little bleeding. The walls of the bed of the tumor were brought together by a purse-string suture, and the peritoneum was closed with a continuous suture. The abdominal wall was closed in layers.

The patient's condition previous to the operation was poor. Immediately after the anesthetic began to be administered, there was a marked drop in the blood pressure; the pulse was very rapid, but the respiratory rate was not increased and the patient was warm. It was the consensus that the operation should proceed. There was practically no change in the condition during the operation. The pulse was rapid and the blood pressure could not be obtained throughout.

After the operation the patient was transferred to her room. Small doses of epinephrine were given every fifteen minutes. The blood pressure still did not

rise. She was rather cyanotic but was warm. She was given inhalations of carbon dioxide and oxygen at intervals. After two and one-half hours, as she had not seemed to react and as her extremities were cold, an intravenous infusion of a 5 per cent solution of dextrose was decided on. The pulse rate began to improve immediately. Her color became better. She regained sufficient consciousness to complain of pain in her right side, for which she was given ⅙ grain (0.0108 Gm.) of morphine sulfate. Just as the intravenous infusion was being finished, she had a sudden attack of pulmonary edema; her lungs filled completely with fluid, and she appeared to drown in her own secretions. Artificial respiration was given, and large quantities of fluid poured out of her mouth, but respiration could not be reestablished, and she was soon dead.

Pathologic Report.—The pathologic examination of the tumor was made by Dr. B. Earle Clarke.

Macroscopic Examination: The specimen consisted of a spherical tumor which measured 9 cm. in diameter. It was covered by a thin fibrous capsule. There were fibrous tags which roughened the surface, but at no place was the capsule broken. From one side there was a flat shelflike projection, which left the surface at an acute angle, so that it tended to parallel the adjacent capsular surface. At its attachment this measured 5 cm. in length. It projected outward 1 cm. and was 3 mm. in thickness. When cut across it presented two layers of yellow cortex enclosing a brownish medulla typical of the normal adrenal gland. The capsule of the tumor was continuous with the capsule of this portion of the adrenal gland, and the glandular tissue became lost in the tumor. In three other places irregular plaques of thinned-out yellow adrenal cortex could be seen through the capsule. The tumor mass was rather soft and dark red.

On section, an eccentrically placed cyst measuring 6 cm. in diameter was noted. This cyst had a thick, dense, fibrous capsule. The lining was smooth and shiny. It was filled with soft, brown granular and amorphous material. There were also smaller cavities, which lacked the thick wall and contained clotted and fluid blood. The solid parts remaining between these cysts were soft, red and hemorrhagic.

Microscopic Examination: The sections were fixed with Zenker's fluid and stained with hematoxylin and eosin. In two sections thin layers of compressed normal adrenal cortex were present on the surface. No normal medulla was demonstrable between this cortical tissue and the tumor. The tumor was vascular. There were numerous small blood-filled spaces, with only endothelial walls. In addition, there were many larger, irregular spaces which had no endothelial lining and were, no doubt, hemorrhagic cysts resulting from necrosis. There was also considerable hemorrhage into the solid parts.

The cells of the tumor varied greatly in size and shape. In general they were large. In places they tended to be spindle-shaped and to form whorls, but for the most part they were solidly massed. There was no tendency to form acini. These cells had an abundance of finely granular cytoplasm. The cell outlines were indistinct and frequently blended to form a syncytium. There were cytoplasmic prolongations. Vacuoles and irregular areas of hyaline degeneration were occasionally noted. I was unable to identify specific hyaline inclusion bodies, such as have frequently been described in such tumors.

The nuclei, too, varied greatly. They were vesicular, and many contained a distinct nucleolus. Frequently they were ovoid or spindle-shaped. Occasionally three or more large nuclei were heaped together, forming a sort of multinucleated giant cell. More frequently there were seen single gigantic nuclei of bizarre shape. No mitotic figures were present.

The stroma was scanty.

Small blocks of the tissue were placed overnight in a 10 per cent solution of potassium di-chromate. Frozen sections of this material showed about half of the cells to be stained brown.

Sections stained by the Giemsa method showed green granules in the cytoplasm, such as are said to be specific for chromaffin cells.

In general the microscopic picture agreed with that of other reported chromaffin cell tumors.

Diagnosis: The diagnosis was pheochromocytoma of the medulla of the adrenal gland.

Report of Biochemical Examination.—Two samples of tumor tissue on analysis were found to contain, respectively, 345 and 353 mg. per hundred grams of wet tissue of reducing substance (calculated as epinephrine).

Vulpian, Comessatti and diazo tests for epinephrine were performed on the extracts prepared from the tissue and found to be positive. A drop of each extract placed on the conjunctiva of a rabbit's eye caused narrowing of the blood vessels and blanching of the area.

A B

Fig. 3.—*A*, the gross specimen before sectioning. The remnant of the normal adrenal gland is distinctively shown. The light spots on the surface are also flattened remnants of the adrenal cortex. *B*, the sectioned gross specimen, showing cystic degeneration.

Two samples were also taken from a central necrotic portion of the tumor. Extracts of these gave negative reactions to tests for epinephrine, and the color in the quantitative determination was of the same order as that observed in the blank determination; so not more than a trace of epinephrine was present in this part of the tumor.

The quantitative method used was a modification of that described by Folin, Cannon and Denis,[4] using the reagent described by Benedict [5] for the determination of uric acid.

4. Folin, O.; Cannon, W. D., and Denis, W.: A New Colorimetric Method for the Determination of Epinephrine, J. Biol. Chem. **13**:477, 1912-1913.

5. Benedict, S. R.: Determination of Uric Acid in Blood, J. Biol. Chem. **51**: 187 (March) 1922; Determination of Uric Acid, ibid. **54**:233 (Oct.) 1922.

Electrocardiographic Findings.—During the last few months of the patient's illness, several electrocardiograms were taken, which revealed unusual abnormalities in the cardiac mechanism. So far as we know, similar abnormalities have not been reported in this condition previously. Previous reports which have included electrocardiographic studies have

Fig. 4.—High power photomicrograph of a section from the tumor. The abundant granular cytoplasm, the indistinct cell boundaries and the tendency to the formation of a syncytium are evident.

usually described a sino-auricular tachycardia, without other abnormality. In the case reported by Coller, Field and Durant [2] the T waves were inverted in leads I and II.

The findings in our case are perhaps best presented by direct reference to the tracings selected for reproduction. In them are included the significant abnormalities observed.

Tracing *A* in figure 5 (the three small strips above) was taken about forty-five minutes after an attack, at a time when the patient had no symptoms. There was still some residual tachycardia (pulse rate 103) from the previous attack, but the tracing is the most nearly normal for this patient that is available. The P waves are unusually high in lead II but less so than during some of the attacks. At such times some of the P waves in lead II were 5 mm. in amplitude.

The longer tracing (*B*) was taken during an attack and revealed coupled beats of rather unusual origin. Every other beat appeared to originate in the auriculoventricular node. These auriculoventricular nodal beats were slightly higher than those of sino-auricular origin and showed a slight notching on the upstroke of the R wave. This abnormality in rhythm apparently arose because the auriculoventricular node for some unknown reason had become more irritable than the sino-auricular node, which in turn appeared to be somewhat depressed. The auricles were beating slowly and regularly at a rate of 55, the interval between auricular beats being 1.1 seconds. The auriculoventricular node escaped at a

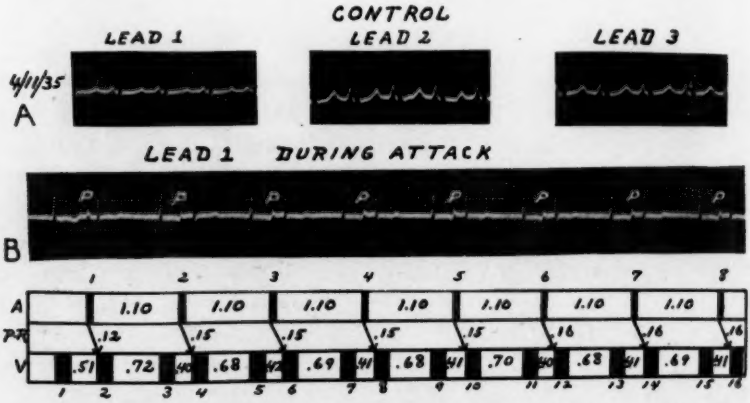

Fig. 5.—The diagrams beneath the longer tracing in figure 5 and the continuous tracing in figure 6 are arranged in identical fashion and may be described together. The black bars in the top strip of the diagram marked "*A*" represent the auricular waves and are placed directly beneath the P waves in the accompanying electrocardiogram. The interval between auricular beats is recorded in hundredths of a second. In the middle strip (marked "P-R") are recorded the PR intervals in hundredths of a second. When conduction of a beat between the auricle and the ventricle is thought to occur it is represented by an arrow. In the bottom strip, marked "V," the heavy black bars represent and are placed directly beneath the ventricular beats. Again the interval between the beats is recorded in hundredths of a second. Tracing *A* was made on April 11, 1935, and tracing *B* on March 30, 1935.

fairly constant interval after the beat of sino-auricular origin (0.68 to 0.72 seconds in *B*). Thus, the auriculoventricular node was considerably more irritable than the sino-auricular node.

Apparently the condition known as unidirectional block was present—that is, beats originating in the auriculoventricular node were not conducted back to the auricles, while beats originating in the sino-auricular node were readily conducted

to the ventricles. Thus the slower sino-auricular node was protected from the faster auriculoventricular node; otherwise the usual type of auriculoventricular nodal rhythm would have resulted.

One of us has on file data concerning several cases in which this disturbance of rhythm occurred, and as a subsequent report on this subject is planned, further discussion of the mechanism involved in this tracing will be deferred.

The abnormality in rhythm shown in figure 6 is similar to that present in figure 5 *B*. The blood pressure was recorded simultaneously with the taking of this tracing and was observed to be 240 systolic and 170 diastolic. Again the auricular

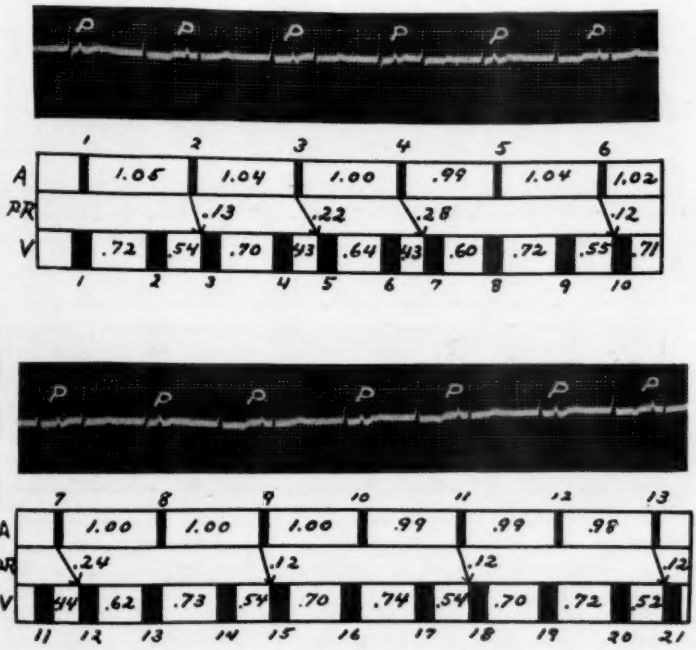

Fig. 6.—A continuous tracing in lead 1 taken on April 6, 1935. The explanation of the accompanying diagram is the same as that for the diagram in figure 5.

rate was slow but not so regular as that shown in figure 5, the interval between P waves varying from 0.98 to 1.05 seconds. As before, the nodal beats were usually higher and more notched than the normal beats, but this was not invariably so, as the nodal beats at times closely resembled those of sino-auricular origin (ventricular beats 1, 6, 8 and 13). The reason for this is not clear.

When the P wave fell shortly after the QRS complex, the ventricles either did not respond at all (auricular beats 1 and 5), or if the RP interval was somewhat longer, responded only after a prolonged PR interval (auricular beats 3, 4 and 7). In the former instance the ventricles were entirely refractory and in the latter partially so. As in tracing *B* in figure 5, the auriculoventricular node

escaped after about 0.7 second—that is, the rhythm during an attack was about 85 beats per minute. The interval between ventricular beats was shorter (for example, the intervals between ventricular beats 7 and 8) after a beat with a long PR interval (ventricular beat 7). This was apparently related to the long PR interval and suggests that the auriculoventricular node had already started to build up a new impulse before the previous excitation wave of sino-auricular origin had completely traversed the lower portions of the partially refractory conducting system.

Figure 7 shows another type of abnormality recorded during an attack of moderate severity. The chief variation from normal was in the P waves. They varied in shape, amplitude and direction. The amplitude of the P waves varied from +4 mm. to −2 mm. As would be expected, the rate was generally faster with the high P waves and slower with the inverted P waves. The high P waves probably originated in the upper portions of the sino-auricular node, while the

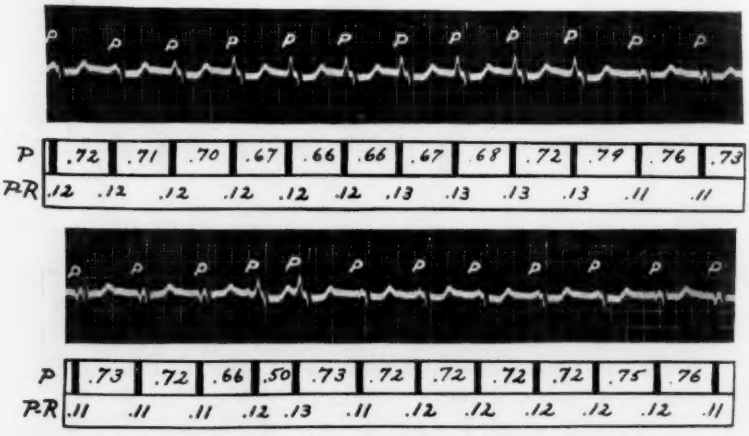

Fig. 7.—A continuous tracing in lead 2 taken on April 16, 1935. In the accompanying diagram the bars in the top strip, marked "P," represent and are placed directly beneath the auricular waves. The interval between beats is again recorded in hundredths of a second. In the strip below, marked "P-R," the PR interval of each auricular beat is recorded beneath that beat in hundredths of a second.

inverted P waves probably arose in the upper portion of the auriculoventricular node. The PR interval was slightly shorter with the inverted P waves than with the tall upright P waves. This supports the suggestion as to point of origin of the waves, as the beats originating in the sino-auricular node have farther to travel before reaching the ventricle. No definite change in the QRS complex was observed.

Comment.—The disturbances of rhythm illustrated in these tracings seemed to result primarily from varying degrees of stimulation of the auriculoventricular node, usually accompanied by varying degrees of depression of the sino-auricular node during attacks. The actual mechanism of this alteration is a matter for speculation. The evidence

at hand suggests that, in this patient at least, the generalized intense stimulation of the sympathetic nervous system that apparently occurs in these attacks stimulates the auriculoventricular node much more than the sino-auricular node.

It is rather probable that in this patient the auriculoventricular node was unusually susceptible to the stimulation occurring in the attacks. If irregularities of the pulse and of the electrocardiographic tracings were a usual part of the syndrome, they would probably have been observed in previously reported cases.

Fluoroscopic Examination.—The pulmonary fields and the diaphragm appeared normal. The left ventricle appeared slightly enlarged in the anteroposterior and left oblique views. The other chambers of the heart and the aorta appeared normal.

During observation the patient had a typical attack of moderate severity. At first, during the period of nausea, the cardiac pulsations were notably diminished in amplitude. At that time the radial pulsation was also very weak. In from one to two minutes the cardiac pulsations became much stronger, and definite irregularities were noted, having the appearance of extrasystoles. This irregularity was also evident on palpating the radial pulse. In another one or two minutes the irregularity disappeared and the heart beat was regular, with good pulsations. The patient was then feeling much better. No definite change in the size of the heart during the attack was detected.

Summary of Electrocardiographic and Fluoroscopic Findings.—Several electrocardiograms are presented and described, illustrating abnormalities that appeared during the attacks characterizing this patient's illness. The site of the formation of the impulse of the heart beat was seen to vary between the sino-auricular and the auriculoventricular node and apparently arose at various locations in these nodes. This appeared to result in this patient from periodic intense stimulation of the auriculoventricular node, at times accompanied by depression of the sino-auricular node. On fluoroscopic examination the outstanding finding was the small amplitude of the cardiac contractions during the early part of an attack, as contrasted with the full, easily visible contractions before and after the attack.

COMMENT

The foregoing case report serves to emphasize certain aspects of the subject. The striking nature of the attacks, especially the sudden transition from hypotension to hypertension, is certainly so different from anything else seen in ordinary clinical experience as to suggest the diagnosis at once to one familiar with the condition. The marked tendency to shock is well illustrated and indicates that surgical intervention, which offers the only hope of recovery, is fraught with the gravest danger. Our experience in this case suggests to us that the abdominal approach must ordinarily be the method of choice, as manipulation of the tumor before its blood vessels are clamped off is likely to be considerable when

a posterior incision is used, and such manipulation must be considered dangerous, as it seems probable that a flooding of the circulatory system with epinephrine may result. In this connection, it is of interest that Pincoffs has called attention to the fact that it is just after the tumor has been separated from the general circulation that profound symptoms of shock are likely to occur and, further, that in one of his patients pressure on the tumor during abdominal examination was always followed by an attack. We feel that if our patient could have been seen in an attack early in the course of the disease and if the condition could have been recognized and operation performed, recovery could have been expected. The brilliant results in some of the reported cases (C. H. Mayo,[6] Coller and his associates [2] and a few others) are encouraging. One is drawn to the conclusion that a favorable outcome depends on adequate surgical treatment after early diagnosis.

As regards the production of the clinical syndrome, it is evident that the symptoms cannot be explained except as a result of activity of the sympathetic nervous system. When one considers that the action of epinephrine is a stimulation of this system resulting in activities typical of sympathetic action and that experimentally the hypertension, vasoconstriction, vomiting, pulmonary edema, shock and death have been shown to result from its injection, one is led to the simple hypothesis that in the case of a pheochromocytoma the blood stream is flooded from time to time with large doses of epinephrine. This idea is supported by the observation in the case reported by Porter and Porter [7] that an attack was always brought on when the patient assumed certain definite positions and that in Pincoffs' patient, as mentioned, when pressure was made on the tumor through the abdominal wall, an attack resulted. In our own patient the occurrence of paroxysms at fifteen minute intervals throughout the greater part of a day while the patient lay quietly in bed is not easy of explanation, nor is the fact that during labor, which was normal, no attack was induced.

SUMMARY

A case is reported of pheochromocytoma of the right adrenal gland with a typical clinical picture, the adrenal sympathetic syndrome and death after operative removal of the tumor.

No improvement was observed after roentgen treatment.

A study of the heart during the paroxysms showed with the onset of the hypertension a slowing of rate with a noticeable increase in

6. Mayo, C. H.: Paroxysmal Hypertension with Tumor of the Retroperitoneal Nerve: Report of Case, J. A. M. A. **89**:1047 (Sept. 24) 1927.

7. Porter, M. F., and Porter, M. F., Jr.: Report of Case of Paroxysmal Hypertension Cured by Removal of Adrenal Tumor, Surg., Gynec. & Obst. **50**: 160 (Jan.) 1930.

the loudness of the sounds and an irregularity of rhythm associated with migration of the pacemaker. It seems probable that many of these changes constitute the cardiovascular reaction to sympathetic stimulation caused by the discharge of large amounts of epinephrine from the tumor into the circulating blood.

In view of the striking clinical picture which these patients present, it is to be hoped that in the future the diagnosis may be suspected early, the condition investigated thoroughly and early operation undertaken. In the more obscure cases we believe that a suspicious clinical picture, with characteristic changes of blood pressure will justify exploratory operation if the diagnosis cannot be made otherwise, in view of the importance of early diagnosis and the possibility of cure by surgical means.

THE ADRENAL GLANDS

A CLINICAL AND PATHOLOGIC STUDY

ERNEST M. HALL, M.D.
AND
LOUISA HEMKEN, M.D.
LOS ANGELES

The relative infrequency of lesions of the adrenal glands becomes apparent when one examines statistical surveys of necropsies. In all probability this accounts for the slight attention given such lesions in the past. Increasing interest in the endocrine glands during recent years, however, has greatly stimulated the study of pathologic changes in the adrenal glands. It is often difficult to establish the presence of lesions of the adrenal glands in the living patient; the symptoms and signs may be indefinite compared to the extent of the lesion observed at autopsy. Again, symptoms referable to the adrenal glands may be obscured by those of a more acute and fulminating disease. During the past six years, in the course of performing routine necropsies, we have collected 39 instances demonstrating pathologic changes in these organs. In view of the fact that knowledge of these glands still remains incomplete, the clinical and pathologic observations made in the 39 instances have been studied. The purpose of this study was to correlate the clinical symptoms with the observations at autopsy, in the hope that the clinician and pathologist in the future might be more alive to the possibility of lesions in the adrenal glands.

The lesions of the adrenal glands in this series may be divided into three groups, as shown in the table. The basis for the division is pathophysiologic. In the first group, symptoms of acute adrenal insufficiency are present. These are often the result of hemorrhages into the adrenal glands. This condition is frequent in the new-born, in whom hemorrhages into both adrenal glands are prone to occur. In older children and in adults acute disturbances of the adrenal glands are not common. The medical literature contains only about one-hundred records of such cases.[1] In this condition the acute symptoms are often attendant on thrombosis of the adrenal veins, with hemorrhagic infarction of the glands. It would appear from a brief survey of the table that hem-

From the Department of Pathology of the University of Southern California School of Medicine, and the Los Angeles County General Hospital.

1. Seligman, Bernard: Suprarenal Hemorrhage in the Adult, with Especial Reference to Hyperpyrexia, M. J. & Rec. **135**:209, 1932.

orrhage into the adrenal glands of adults is far from rare. It is interesting to note that greater numbers of such hemorrhages are recorded in the recent medical literature. This does not imply an absolute increase in the incidence but is the result of more accurate and detailed observations on the adrenal glands.

The second group, which includes the growths in the majority of cases, takes into consideration those adrenal lesions which are of a more chronic nature. The average duration is one year and may be as long as three years. Addison's disease is the classic example. The addisonian syndrome is usually due to tuberculosis of the adrenal glands, although other causes, such as atrophy, may operate to give a similar clinical picture. When the records of large series of autopsies were examined it was found that the incidence of Addison's disease was less than 1 per cent. In Ophüls' [2] series of 3,000 autopsies there were 13 instances

Pathophysiologic Classification of Lesions of the Adrenal Glands

A. Acute adrenal insufficiency	
I. Hemorrhage	
(*a*) In the new-born	4
(*b*) In older children	1
(*c*) In adults	5
B. Chronic adrenal insufficiency	
(*a*) Atrophy	5
(*b*) Simmonds' disease	1
(*c*) Addison's disease	5
(*d*) Coccidioidal granuloma	1
(*e*) Secondary neoplasm	3
C. Chronic adrenal hyperfunction	
I. Hypertrophy	
(*a*) Diffuse	1
(*b*) Compensatory	1
II. Cortical neoplasm	
(*a*) Adenoma	11
(*b*) Carcinoma	1

(0.43 per cent) of Addison's disease. In 1924 in the registration area of the United States 363 deaths (0.3 per cent) were ascribed to Addison's disease of a total of 1,173,990.[3] A review [4] of 25,000 autopsies performed at the Philadelphia General Hospital from 1867 to 1932 showed 55 (0.22 per cent) cases in which tuberculosis of the adrenal glands was observed, with symptoms of Addison's disease in only 11 (0.04 per cent). A series of 12,000 necropsies from the Leeds General Infirmary [5] showed 24 cases that revealed tuberculosis of the adrenal

2. Ophüls, William: A Statistical Survey of Three Thousand Autopsies, Stanford University, Calif., Stanford University Press, 1926, p. 297.

3. Guttman, P. H.: Addison's Disease: A Statistical Analysis of Five Hundred and Sixty-Six Cases and a Study of the Pathology, Arch. Path. **10**:742 (Nov.); 895 (Dec.) 1930.

4. Clark, J. H., and Rowntree, L. G.: Studies of the Adrenal Glands in Health and Disease, Endocrinology **18**:256, 1934.

5. Hellier, F. F.: The Incidence of Atrophy and Tuberculosis of the Adrenal Glands and Their Relation to Addison's Disease, J. Path. & Bact. **33**:761, 1930.

glands, but an addisonian syndrome occurred in only 9 instances (0.075 per cent). At the University College Hospital, London, 5,195 autopsies showed a total of 23 (0.44 per cent) deaths from Addison's disease.[6]

The third group includes benign and malignant neoplasms. The patients occasionally exhibit signs and symptoms of chronic hyperfunction of the adrenal glands. Hypertrophy of one adrenal gland is sometimes observed when the opposite gland has been destroyed by hemorrhage or tuberculosis. Simple bilateral hypertrophy is rare. Cortical adenoma is of relatively frequent occurrence, as shown in the table, but in many instances it does not produce any detectable clinical evidence of its presence. Geschickter[7] collected 72 instances of tumor of the adrenal cortex; 66 growths were benign adenomas, and the remaining 6 were carcinomas. In our series there is 1 example of carcinoma of the adrenal cortex, but primary tumor of the adrenal medulla is not represented.

ACUTE ADRENAL INSUFFICIENCY

In the New-Born.—Extensive destruction of both adrenal glands by hemorrhage is inevitably fatal. This may occur in the absence of other lesions in other parts of the body. The clinical course is usually short. The diagnosis is difficult; it has been made in only a few instances during life. The presence of acute adrenal dysfunction should be suspected in fever of unknown origin, especially when it is associated with an increased rate of respiration and normal pulmonary findings. A yellowish pallor, cyanosis of the lips and finger-tips and a palpable mass in each flank are confirmatory signs.

Severe and fatal hemorrhage of both adrenal glands was encountered in the bodies of two new-born infants. It is interesting that these patients were identical twin girls (baby M.1 and baby M.2). Their symptoms, for the short duration of their lives, and the observations at autopsy were practically identical. Both were born at full term and were fairly well developed. At the time of delivery the respirations were slow and shallow and the heart sounds weak. Marked cyanosis of the visible mucous membranes and of the finger-tips was observed several hours after birth. One infant lived six, and the other eighteen, hours. At necropsy the lesions were confined to the adrenal glands. These were about three times larger than normal and contained much clotted blood. Microscopic examination of one adrenal gland showed widespread hemorrhage of recent origin in the medulla, with extension throughout the greater part of the cortex. The cortical cells were in various stages of degeneration, and only in a few small regions where there was little or no hemorrhage did they appear healthy. An interesting observation was the presence of small thrombi in some of the veins of the medulla.

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6. Barnard, W. G.: Adrenal Atrophy in Addison's Disease, J. Path. & Bact. **33**:765, 1930.

7. Geschickter, C. F.: Suprarenal Tumors, Am. J. Cancer **23**:104, 1935.

The prognosis is more favorable when the adrenal hemorrhage is unilateral. It is therefore important that the clinician be able to recognize the signs and symptoms of adrenal insufficiency. Spontaneous recovery usually occurs if the hemorrhages are small. Massive unilateral hemorrhage often causes the same symptoms as bilateral hemorrhage. The presence of a mass in each flank makes the diagnosis of adrenal hematoma relatively certain. Intramuscular injections of whole blood may lead to recovery.[8] The administration of adrenal cortex hormone combined with blood transfusions may tide the infant over until organization of the hemorrhage has occurred or, perhaps, until the accessory cortical tissue has had an opportunity to undergo compensatory hypertrophy.[9] Intestinal obstruction in one instance was the result of pressure from a huge adrenal hematoma; excision of the mass led to recovery.[10] Hemorrhage of moderate severity in the adrenal glands may be associated with ecchymoses in other parts of the body. The adrenal hemorrhage may be only one manifestation of hemorrhagic diathesis in the newborn.

In an apparently normal boy (baby J.) cyanosis and difficulty in respiration occurred several hours after birth. The administration of whole blood and dextrose caused some improvement. A second blood transfusion was given, with similar beneficial results. The cyanosis became extreme, and the infant died about one day after birth. At autopsy, the right adrenal gland was softened and hemorrhagic in the central portion; the left adrenal gland appeared normal. The adrenal lesion was complicated by moderate subdural and subtentorial hemorrhages. This combination of conditions was no doubt responsible for the fatal outcome. In another boy (baby C.) respiration was established with difficulty. Death occurred shortly after birth. The left adrenal gland was soft and hemorrhagic, with necrosis of the medulla and the inner two thirds of the cortex. The right adrenal gland was grossly normal, but microscopic examination revealed congestion and a number of small hemorrhages in the cortex. A small subtentorial hemorrhage was the only other lesion in the body.

In the summation of these four records, two important common denominators are noted, viz., the difficulty in respiration and the cyanosis of the visible mucous membranes and the finger-tips. The temporary improvement brought about by blood transfusions in one baby is significant. It appears plausible that the administration of cortical hormone might have saved this infant's life, especially since the adrenal hemorrhage was unilateral and the cerebral injury slight.

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8. Rosenblum, Jacob: Suprarenal Hemorrhage in the New-Born Infant, Am. J. Dis. Child. **43**:663 (March) 1932.

9. Goldzieher, M. A., and Greenwald, H. M.: Hemorrhage of the Suprarenals in the New-Born Infant: Diagnosis and Therapy, Am. J. Dis. Child. **36**:324 (Aug.) 1928.

10. Corcoran, W. J., and Strauss, A. A.: Suprarenal Hemorrhage in the New-Born, J. A. M. A. **82**:626 (Feb. 23) 1924.

In Older Children.—In older children punctate hemorrhages in the adrenal glands occur frequently during the course of infectious diseases. Larger hemorrhages are relatively uncommon and when they do occur are usually secondary to adrenal necrosis resulting from bacterial action or the effect of bacterial toxins.

A dramatic illustration of extensive bilateral adrenal hemorrhage was observed in a 5½ year old boy (W. D.). Vomiting occurred suddenly, and within a few hours the patient became stuporous and cyanotic. The respirations were rapid, and a few râles were audible over the base of the right lung. The neck was rigid; the cerebrospinal fluid eight hours after the onset of symptoms was normal. The child failed to rally, despite the administration of antimeningococcus serum and cardiac stimulants. He died twelve hours after the onset of the clinical symptoms. At the autopsy both adrenal glands were completely infiltrated with blood. Microscopically, necrosis was evident in the cortical tissue. There was bilateral hemorrhagic bronchopneumonia, and in the meninges were small collections of purulent material from which a few diplococci were recovered on direct smear but none on culture. The fatal outcome was attributed to the adrenal hemorrhage, which occurred in the beginning of fulminating cerebrospinal fever.

In Adults.—In adults hemorrhage into the adrenal glands most often follows thrombosis of both adrenal veins.[11] This is more likely to occur in persons with chronic heart disease or long-standing tuberculosis or during the course of an acute infectious disease. At times bacterial emboli[12] may be demonstrated in the small adrenal arteries.

It is difficult and usually impossible to recognize the existence of an adrenal hematoma during life. Symptoms may be absent.[13] Hemorrhage, however, may be suspected in persons who complain of severe abdominal pain in the absence of physical signs, especially during the course of an acute infection. Asthenia, accompanied by a gradual fall in the blood pressure and a rise in the temperature, is observed at times. When bilateral hemorrhagic infarction of the adrenal glands occurs in the course of an overwhelming infection, the symptoms of the latter may completely mask any signs of acute adrenal disturbance. This happened in an otherwise normal and healthy white man.

In J. K., 33 years of age, the usual signs of lobar pneumonia were first detected in the lower lobe of the right lung, the process spreading within a few days to all the pulmonary fields. Death occurred nine days after the onset. The lungs, with the exception of the upper lobe of the left lung, were in a state of gray hepatization. Both adrenal glands were from three to four times larger than

11. Simmonds, M.: Ueber Nebennierenblutungen, Virchows Arch. f. path. Anat. **170**:242, 1902. Dudgeon, L. S.: On Etiology, Pathology and Diagnosis of Adrenal Hemorrhage, Am. J. M. Sc. **127**:134, 1904. Pearl, F., and Brunn, H.: Suprarenal Apoplexy, Bilateral, Surg., Gynec. & Obst. **47**:393, 1928.

12. Kovács, Andreas: Beiderseitige akute Nebennierenblutung bei Influenza, Frankfurt. Ztschr. f. Path. **38**:387, 1929.

13. Arnaud, F.: Les hémorragies des capsules surrénales, Arch. gén. de méd. **4**:5, 1900.

normal (fig. 1). This increase was due to extensive recent hemorrhage. Microscopic examination showed that the medulla was distended with blood, and the large veins contained hyaline thrombi from 1 to 3 mm. in diameter. The cortex contained recent extravasations of blood in all parts, and there was marked necrosis of much of the cortical tissue. The fibrils of the adrenal capsules were spread apart by hemorrhage, and in many places bleeding had extended far beyond the capsular boundaries. Sections stained by the Gram-Weigert method failed to reveal any organisms.

Severe abdominal pain developed in a man (D. F. R.), 40 years of age, who had apparently made a complete recovery after an attack of acute streptococcic tonsillitis. This soon became worse and was most severe in the region of the left kidney. The patient was extremely restless. Rigidity developed on the left side of the abdomen. Severe pain was then experienced on the right side, so that exploratory laparotomy was deemed advisable. No abdominal lesions were observed. The patient became progressively weaker; the pulse rate became more rapid, and the temperature rose to 104.6 F. Death occurred two days after the

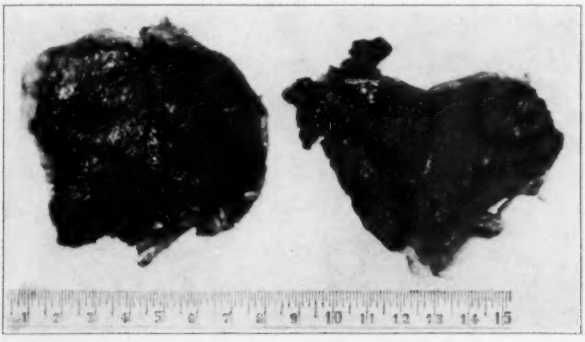

Fig. 1 (J. K.).—Massive hemorrhage in both adrenal glands, secondary to lobar pneumonia.

operation. The only lesions to be seen at autopsy were in the adrenal glands. Both adrenal glands were embedded in hematomas, and the glandular tissue was apparently necrotic (fig. 2). Microscopically, both glands and much of the surrounding connective tissue were densely and diffusely infiltrated with blood. Except for the presence of a few islands in the cortex, the epithelial cells were completely destroyed. In a number of places the capsule appeared to be heavily infiltrated with neutrophils. Many of the veins in the surrounding connective tissue, as well as those in the glands themselves, were filled with recent thrombi.

Adrenal hemorrhage was also observed in an 18 year old girl (R. T.). This occurred in the early months of the patient's first pregnancy, which was complicated by severe hyperemesis gravidarum. The sole lesion was in the adrenal glands. There was extensive hemorrhage into the medulla and cortex of the left adrenal gland, while several smaller hemorrhages were observed in the gland on the right. The microscopic picture resembled in many respects those described in the preceding records. In this case also the medulla was distended by a recent

extravasation which was infiltrated in several places by large collections of polymorphonuclear leukocytes. Two large veins and a few smaller ones in the medulla were almost completely filled with thrombi.

Ecchymoses into the adrenal glands may be observed during the course of careful postmortem examinations in persons who have died of a variety of lesions. Such hemorrhages are not extensive. They do not give rise to symptoms, as a rule, but are included in this series because they demonstrate the relatively frequent occurrence of hemorrhage in the adrenal glands of adults.

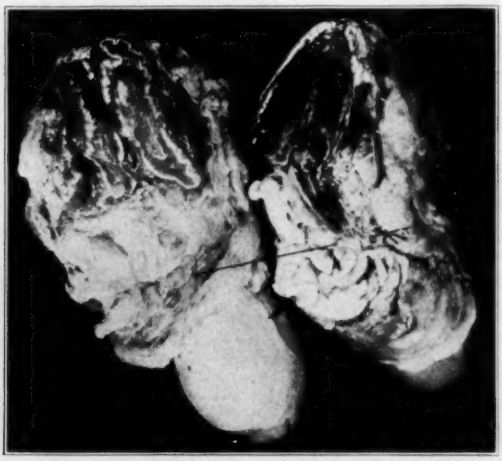

Fig. 2 (D. F. R.).—Massive bilateral hemorrhage in the adrenal glands, secondary to tonsillitis (streptococcic).

In a man (V. B.), of 63 years, with aleukemic myelogenous leukemia microscopic examination revealed small hemorrhages in the medulla and the deeper parts of the cortex. Hyaline thrombi were seen in some of the arterioles and smaller veins. In another man (J. Y.), 76 years of age, in whom there was a carcinoma of the prostate, with extension and metastases, moderate hemorrhage had occurred into both adrenal glands. In many places the cortex was completely necrotic, while the medulla was well preserved.

CHRONIC ADRENAL INSUFFICIENCY

Atrophy.—The term chronic adrenal insufficiency is nearly always associated in the physician's mind with a tuberculous process in the adrenal glands. This destructive lesion frequently results in the definite and well recognized clinical picture of Addison's disease. At postmortem examination, however, in about one tenth of the persons who had signs of an addisonian syndrome during life the adrenal glands will be seen to be small, with no demonstrable evidence of tuberculosis.

The pathologic changes in many of these small atrophic glands are confined to the cortex, while in others extensive lesions are present in both the cortex and the medulla. Many names have been suggested for the condition, and one finds the lesions referred to as hypoplasia, simple or idiopathic atrophy, cirrhosis and cytotoxic contraction or primary contraction of the adrenal glands.[3] This variability in terminology reflects the present ignorance of the underlying pathologic process. Congenital hypoplasia of the adrenal glands has been suggested as a possible cause, but there are no facts to support this theory. Healed tuberculous processes with extensive scarring are also a theoretical possibility. There has been no proved instance of healed tuberculosis of the adrenal glands.[3] Syphilitic infections have been incriminated without an adequate pathologic basis for such a contention.[14]

There is a striking resemblance between atrophy of the adrenal glands and toxic necrosis of the liver, especially in the group of subchronic lesions. This suggests that a toxic agent may act selectively on the cells of the adrenal cortex [15] in much the same manner as certain poisons are believed to destroy the liver cells. The toxic agent which is thought to injure the adrenal cortex must be continuous or at least intermittent in its action over a considerable period. Lesions in the medulla are secondary to those in the cortex. In the end the regenerative capacity of the cortex may become inadequate, and clinical evidence of adrenal insufficiency becomes apparent. There is no evidence as to the nature of the agent which brings about slow degeneration of the cortical cells. One must conclude that the etiology is still unknown. Accurate pathologic studies of adrenal glands showing primary contraction are of value in determining the functions of the adrenal cortex and the medulla. Such studies should also give a better understanding of the underlying forces operative in the production of the addisonian syndrome.

The medical literature contains a series of interesting records of primary contraction of the adrenal glands.[16] Of some import, perhaps,

14. Simmonds, M.: Ueber Nebennierenschrumpfung bei Morbus Addisoni, Virchows Arch. f. path. Anat. **172**:480, 1903.

15. Kovács, Walther: Zur Nebennierenpathologie, Beitr. z. path. Anat. u. z. allg. Path. **79**:213, 1928.

16. (*a*) Bittorf, A.: Die pathologie der Nebennieren und der Morbus Addisoni, Jena, Gustav Fischer, 1908. (*b*) Conybeare, J. J., and Millis, G. C.: Observations on Twenty-Nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, Guy's Hosp. Rep. **74**:369, 1924. (*c*) Harbitz, F.: Suprarenals in Addison's Disease, Norsk mag. f. lægevidensk. **87**:371, 1926. (*d*) Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, Quart. J. Med. **85**:121, 1928. (*e*) Barker, Nelson W.: The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, Arch. Path. **8**:432 (Sept.) 1929. (*f*) Wells, H. Gideon: Addison's Disease with Selective Destruction of the Suprarenal Cortex ("Suprarenal Cortex Atrophy"), ibid. **10**:499 (Oct.) 1930.

is the series of 9 cases of Addison's disease studied by Wells[10f]; in 6 the condition was of the atrophic type, and in only 3, of the tuberculous type. In the former there was nothing either in the clinical history or in the pathologic studies to explain the widespread destruction of the adrenal glands. A possible relation between influenza and adrenal atrophy is suggested. Many records will have to be examined before conclusions of value can be reached regarding the etiologic significance of influenza or other infections in the production of primary contraction of the adrenal glands.

There are no constant clinical features in Addison's disease which differentiate a tuberculous process from atrophy. Minor differences may be noted at times, which may favor either one process or the other. At times the blood pressure, although reduced, is at a relatively higher level in persons suffering from adrenal atrophy. The higher pressure is attributed to a relative integrity of the medulla. Shortly before death the blood pressure usually sinks to a low level. Frequent blood pressure readings in cases of Addison's disease may be of value. Pigmentation of the skin has been the only clinical feature observed over a period of several years in some persons with primary contraction of the adrenal glands; occasionally a dark skin has been present since childhood. Unfortunately, chronic adrenal insufficiency is not always accompanied by darkening of the skin, and it is in this group that there is the greatest difficulty in diagnosis.

The relative infrequency of primary contraction of the adrenal glands and the unrevealed etiology are sufficient reasons for reporting the present series of five records. Pigmentation and clinical signs of adrenal insufficiency were present in 2.

In a woman (P. C. T.), 50 years of age, who had always had a dark skin, pigmentation had become more noticeable during the last two years of life. The increase in pigmentation followed an attack of influenza and was associated with progressive weakness, and the blood pressure was apparently low. Gastrointestinal disturbances were present a few days before death. It is interesting that this woman was seen by a physician for the first time only two days before her death. She appeared well developed and well nourished. Pigmentation was observed in the skin of the face, neck, forearms and inner surfaces of the elbows and thighs and on the labia. The general condition seemed fair, but she died suddenly and unexpectedly. At autopsy the right adrenal gland appeared to be absent. The left gland, which was very small, measured 2 by 1.5 by 0.3 cm. Sections from the region of both adrenal glands showed small remnants of the cortex and medulla surrounded by dense cicatricial tissue, heavily infiltrated by round cells. There was hypertrophy of the cortical cells, some having developed into giant cells (fig. 3). The small adrenal glands were associated with brown atrophy of the heart and atrophy of the ovaries and the breasts.

In another strongly built and well nourished woman (H.), 50 years of age, pigmentation of the skin, weakness, loss of weight and nervousness were present for one year. Rest in bed failed to improve the general condition. She became

progressively weaker and had attacks of syncope. Precordial pain and a friction rub over the cardiac area led to a diagnosis of acute pericarditis. The blood pressure was 110 systolic and 80 diastolic; the skin was scaly, and the tissues were flabby. Hypothyroidism and hypo-adrenia were suspected. Thyroid extract administered by mouth and epinephrine hydrochloride given intramuscularly improved the general condition, but the precordial pain and anginal attacks persisted, so that the patient was kept in bed. Terminal bronchopneumonia hastened her death. Autopsy showed a normal pericardium and moderate but generalized senile arteriosclerosis, with some cardiac hypertrophy. Each adrenal gland was embedded in adipose tissue and was from one-half to two-thirds the normal size.

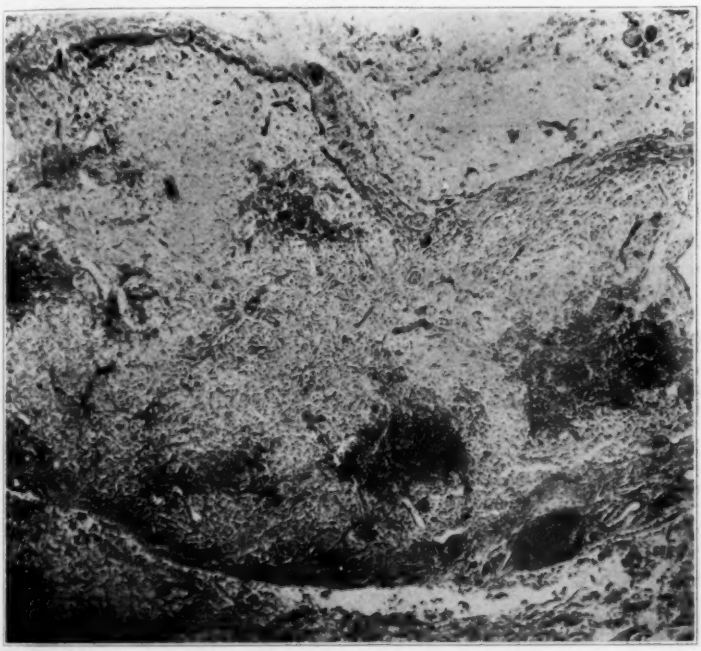

Fig. 3 (P. C. T.).—Photomicrograph showing chronic adrenalitis with atrophy and fibrous thickening of the capsule. The zonal architecture of the cortex is completely obliterated.

Microscopically, the capsule was thickened, and there were a few lymphocytes between the fibrils. In the thinner portions of the gland there was no medulla, and the cortex was decreased in width, although there was a suggestion of the usual layers. The pale cortical cells contained considerable lipoid. Relatively large islands of medullary cells were present in the thicker portions of each gland. With connective tissue stains some increase in the fibrous stroma was apparent in both the cortex and the medulla.

The following clinical history of a 32 year old woman (M. C.) who died suddenly during the administration of an anesthetic is very instructive: All her

complaints dated from the birth of a child ten years previously. At this time a "physical and mental breakdown" occurred. Labor had been prolonged but was normal in all other respects. After an attack of influenza a year previously she regained her strength very slowly. At the time of her last admission to the hospital she complained of a tired feeling and a bearing-down sensation in the lower part of the abdomen. She appeared very nervous. There were a cystocele, a rectocele and a shallow cervical tear. The blood pressure was 98 systolic and 78 diastolic, and the pulse rate was 100. With rest in bed the systolic pressure rose to 115 mm. of mercury, and the pulse rate varied between 74 and 80. The patient became less nervous and appeared to be in good condition for an operation. Thirty grains (0.2 Gm.) of chlorbutanol was given preoperatively. The

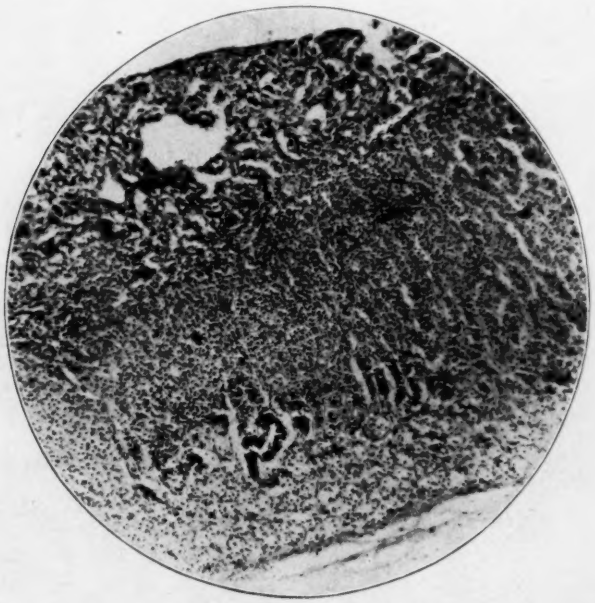

Fig. 4 (M. C.).—Photomicrograph showing marked atrophy of the adrenal cortex. This is true atrophy, with diminution in size of the individual cells. The various layers are poorly defined.

pulse was of good volume. Nitrous oxide gas was not tolerated well; the skin became dusky, and the respirations slow. Ethylene was substituted, but after a few minutes the pulse stopped. Artificial respiration and stimulants were of no avail.

Autopsy showed cyanosis of the lips, ears and neck. The left adrenal gland measured 2.5 cm. in length and 4 mm. in the thickest portion. The right gland was slightly smaller and was only 2 mm. in its thickest part. Microscopically, the capsule was thickened. The zonal arrangement of the cortex was disturbed, and all the cortical cells were small (fig. 4). The medulla consisted of only one or two small groups of cells. The right adrenal gland contained a few

minute cortical adenomas. These changes in the adrenal glands were associated with fatty changes in the liver, lipomatosis of the wall of the right ventricle of the heart and slight chronic bronchitis with peribronchial scarring.

The past history suggested that this patient had always been below par. She had been delicate as a child and had had rickets. When she was 11 years of age an acutely inflamed appendix was removed. At the age of 15 a "nervous breakdown" occurred. It seems logical to conclude that in this patient a moderate degree of adrenal insufficiency had been present for a number of years.

A woman (J. S.), of 38 years, had complained of dysmenorrhea for the past five years. The pain had become progressively severe. She had noticed a mass in the lower part of the abdomen about one and one-half years before consulting

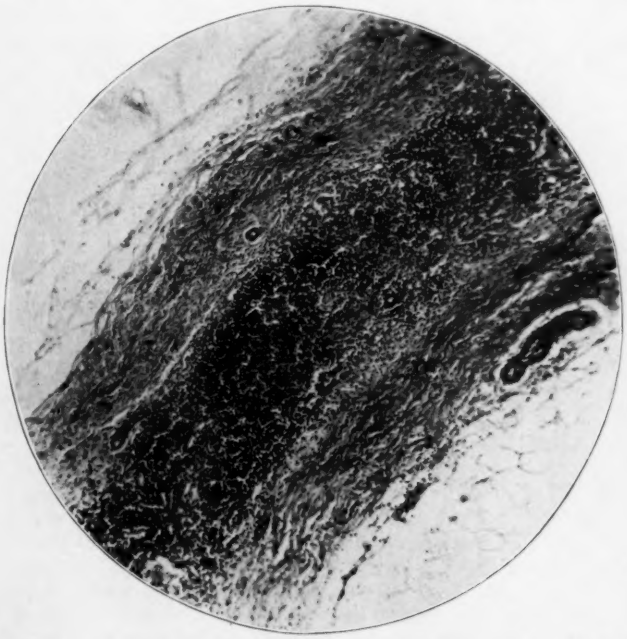

Fig. 5 (J. S.).—Photomicrograph showing chronic inflammation of the adrenal gland, with marked capsular fibrosis and heavy diffuse infiltration by round cells.

a physician. Examination revealed a firm nodular mass filling the pelvis. The blood pressure was 118 systolic and 72 diastolic. An operation was performed, and the uterus was removed. This was large, with several fibromyomas and bilateral ovarian cysts.

Soon after the operation the pulse became soft and very rapid and the hands cold and clammy. Fluids were given by hypodermoclysis, and the patient showed improvement. Late in the afternoon of the day of the operation sudden extreme shock with mild cerebral irritation occurred. Immediate improvement followed the intracardiac injection of 2 cc. of a 1:1,000 dilution of epinephrine hydrochloride. Early in the evening the patient again went into shock. The intracardiac

injection of epinephrine hydrochloride resulted in some improvement, and from 15 to 20 minims of epinephrine hydrochloride was then given intravenously every forty-five minutes. With each injection transitory improvement was observed. The skin became an icteric color, and twitching of muscles and delirium occurred. The patient died about fifteen hours after the operation. At the necropsy the only evident lesions were in the adrenal glands, the right one being extremely small, with a thin cortex and softening of the central portion. The left gland was about one-third the normal size and only 2 mm. in thickness. In the microscopic study the capsules of the glands were densely fibrous, with heavy collections of lymphocytes replacing the glandular tissue (fig. 5). The cortex was almost completely destroyed except for a few small islands of regenerated cortical cells. There was no medulla.

A woman (M. L.), of 43 years, had recurrent attacks of epigastric pain for the last ten to fifteen years. During the last year there was much nausea, which was sometimes associated with vomiting. There was some radiation of pain to

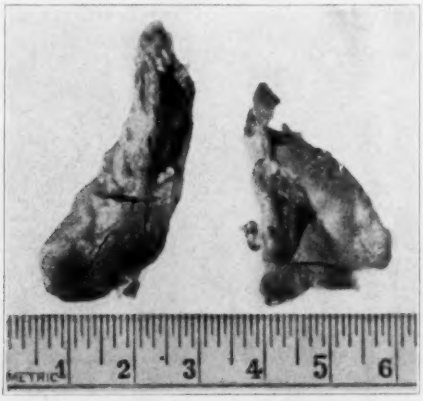

Fig. 6 (M. L.).—Atrophy of the adrenal glands.

the back. The patient was small, weighing only 100 pounds (45.4 Kg.). The blood pressure was 95 systolic and 60 diastolic. Roentgen examination suggested pyloric obstruction from a healed ulcer. Surgical intervention for the alleviation of symptoms was deemed advisable. Numerous gallstones were removed from the gallbladder, and a gastro-enterostomy was done. She died suddenly and unexpectedly one month after the operation. At the postmortem examination signs of terminal bronchopneumonia with acute serofibrinous pleuritis were present. A small abscess was observed in the region of the surgical incision. There was chronic cholecystitis. The pylorus and duodenum were drawn up and fixed to the gallbladder by dense adhesions. The pyloric opening was small. There had been good healing of the gastro-enterostomy wound. The left adrenal gland weighed 2.6 Gm., and the right, 1.8 Gm. (fig. 6). Sections through the adrenal glands showed thickened capsules. The cortex was extremely narrow, and the cells had a disorderly arrangement. Small islands of medullary tissue were seen.

Simmonds' Disease.—Polyglandular disease, or Simmonds' disease, is usually associated with small adrenal glands. There may be some

difficulty in differentiating between Simmonds' disease and the addisonian syndrome clinically, particularly when pigmentation of the skin, hypotension and marked asthenia are present.

Polyglandular disease was observed in a woman (R. R.) of 40 years. Her chief complaints were weakness and inability to withstand cold. She had the appearance of an emaciated woman of about 70 years. Her skin was yellow and dry, and there was a brown patchy pigmentation of her face. The scalp hair was very fine; axillary and pubic hair was absent. There was marked hypotension; the blood pressure was 80 systolic and 60 diastolic. A clinical diagnosis of Simmonds' disease was made, although Addison's disease was considered. The patient's weakness increased progressively until death.

At the postmortem examination all that could be seen of the pituitary gland was a small gelatinous residue of the posterior lobe. There was marked atrophy of most of the organs. The thyroid gland was small and weighed only 10 Gm., while the liver weighed 620 Gm. and the weight of the combined kidneys was 160 Gm. There was marked atrophy of the ovaries, uterus, vagina and mammary glands. The adrenal glands were about one-third the normal size. Microscopically, both had capsules of dense connective tissue. The cortex was absent in some places, and in others three layers were present. Many of the cortical cells were necrotic. The medullary cells were indefinitely outlined, and most of the nuclei appeared pyknotic. In the left gland the medulla was almost completely absent and was replaced by connective tissue markedly infiltrated with round cells.

Addison's Disease.—Addison's disease usually results from tuberculosis of both adrenal glands and produces a well recognized clinical picture. The salient features are illustrated in the following brief clinical and pathologic records:

The chief complaints of a woman (D. B.), of 33 years, were general weakness, loss of weight and gastric disturbances. These symptoms had become more pronounced following an attack of influenza seven months before death. Darkening of the skin was first noticed after this infection. She was fairly well developed and showed splotchy pigmentation of the neck, back, abdomen and extremities. The buccal mucosa was also pigmented. There was atrophy of the muscles of the extremities. Blood pressure readings were consistently low; the systolic pressure was 88 mm. of mercury ten days before death and gradually dropped to 76 mm. A clinical diagnosis of Addison's disease was made.

At the autopsy both adrenal glands were large; confluent regions of caseous necrosis were seen grossly, but normal adrenal tissue was not in evidence. Microscopically, caseous areas were bounded by fibrous tissue containing many round cells and a few cellular tubercles. No adrenal tissue was observed. Smears contained many acid-fast bacilli. There were small partially healed tuberculous foci in the lungs and peribronchial lymph nodes and evidence of active tuberculosis in the ileum.

In a woman (F. D.), of 40 years, the major complaints were weakness and loss of weight. The onset occurred a year previously, with pain in the joints and severe infection of the teeth and gums. At the time of her last admission to the hospital she was greatly emaciated. There was brown pigmentation of the skin of the hands and elbows. The teeth were loosened by the existing purulent gingivitis. She became irrational, requiring restraint, and died shortly after admission. Large adrenal glands weighing 40 Gm. were observed at the autopsy. The

normal architecture was replaced by homogeneous grayish firm tissue. A few regions of caseation were visible in the left gland. Microscopically, there was much tuberculous granulation tissue containing many solitary and confluent tubercles abounding in giant cells. A few areas of caseation were noted, and these were surrounded by dense fibrous tissue. A Ghon tubercle was noted in the apex of the left lung. The heart and aorta were hypoplastic; the thymus measured 7 by 6.5 by 1 cm.

The third observation was made on a man (H. H.), 58 years of age, who had complained of progressive weakness for the past nine months. During the last few weeks he had been recumbent most of the time. There were a feeling of coldness of the extremities and extreme nausea at the sight of food. The skin over most of the body was burned brown by the sun, but shortly before death this pigmentation increased. The systolic pressure was very low (80 mm. of mercury). There was weakness of the extremities, and muscle tone was deficient. Although the patient rallied somewhat after a blood transfusion and a subcutaneous injection of extract of adrenal cortex, he continued to become weaker, lapsing into a state of drowsiness just before death.

Both adrenal glands were of normal size but had irregular contours and contained firm caseous regions which had apparently replaced all the normal glandular tissue. Histologically, large caseous areas were surrounded by tuberculous granulation and fibrous tissue (fig. 7). Narrow bands of cortical cells were seen in the right adrenal gland but were not present in the left. Focal, partially healed tuberculous lesions were observed in the apex of both lungs and in the peribronchial lymph nodes.

Extensive destruction of the adrenal glands by tuberculosis does not always give rise to definite symptoms. Patients with this condition may die suddenly in the same manner as those with primary contraction of the adrenal glands. This is shown in the following observation:

A man (T. M.), 39 years of age, consulted a physician because he had noticed blood in the urine. At times he had had protracted chills after urination, and these had always left him weak and exhausted. Physical examination revealed dark pigmented areas on the face, hands, back and abdomen. The gums and buccal mucosae were also pigmented. The blood pressure was 115 systolic and 50 diastolic. Pyelograms failed to outline the calices of the lower pole of the right kidney. The left kidney produced a normal shadow. Nephrectomy was performed. The right kidney had a large solitary cyst in its lower pole. The patient died suddenly the morning after the operation. At the postmortem examination the adrenal glands were seen to be normal in size but showed irregular areas of caseation. Histologically, these were surrounded by fibrous tissue and contained some atypical tubercles. A small remnant of adrenal tissue was seen in only one place. There were signs of terminal acute hemorrhagic bronchopneumonia, and small, apparently quiescent, tuberculous foci were present in the apexes of both lungs.

It may occasionally be difficult, even impossible, to determine the etiologic agent which has destroyed a great part of the suprarenal tissue.

In a man (A. H.), of 64 years, the usual signs and symptoms of prostatic hypertrophy were present. A first blood pressure reading revealed moderate hypotension, the pressure being 120 systolic and 78 diastolic; two subsequent readings were 100 systolic and 65 diastolic and 105 systolic and 70 diastolic, respectively. The histamine skin test for adrenal function was unsatisfactory. A first stage operation for an enlarged prostate gland was withstood well, and the systolic

pressure on the subsequent days remained between 120 and 124 mm. of mercury. The second stage operation was performed nine days after the first one. Soon after the operation the patient passed into profound shock; the pulse rate became rapid (from 140 to 150), and death occurred two days later. At the autopsy a brownish mottling of the skin of the abdomen and about the external genitalia was noted. The interesting lesions were in the adrenal glands. The left gland was represented by a calcified scar and one or two small bits of adrenal cortex. The right gland was about normal in size and measured 4.5 by 3 by 0.3 cm. It contained one small region of calcification and a small adenoma. Microscopically, the left adrenal gland had a thickened fibrous capsule; there was only a small amount of degenerated cortical tissue remaining, which was surrounded by fibrous tissue and heavy calcific deposits. In the right gland a goodly amount of cortical tissue was present; the cortical cells contained many tiny globules of fat, which were much smaller and more diffuse than the normal globules of lipoid. Dense

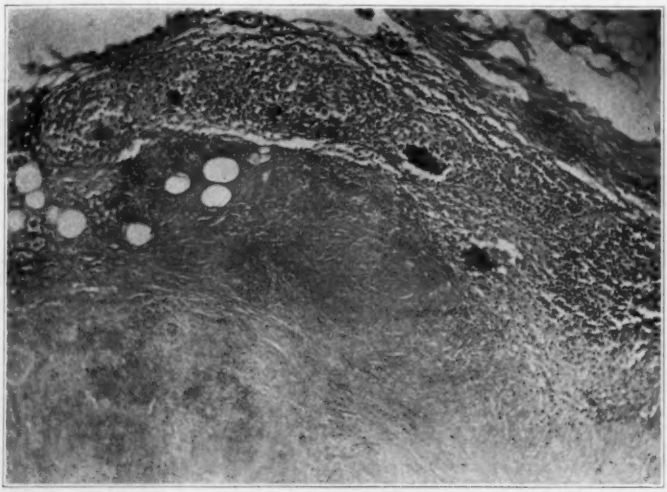

Fig. 7 (H. H.).—Photomicrograph showing a typical area of a tuberculous adrenal gland. A large area of caseation is bordered by tuberculous granulation tissue in which small tubercles and several Langhans giant cells are seen.

fibrous tissue containing many round cells had grown between the cortical cells, and there were two small regions of calcareous degeneration. The medulla was reduced in amount, and in its place were many round cells. A small, partially healed tuberculous focus in the apex of the left lung was the only evidence of past infection.

Coccidioidal Granuloma.—The record of a woman (I. H.), 45 years of age, deserves mention. Symptoms suggesting pulmonary tuberculosis had been present for about three months. These were complicated by meningitis in the last two weeks of life. Coccidioides immitis was demonstrated in cultures of the spinal fluid and in those of material from an enlarged posterior auricular lymph node one week before death. At the necropsy lesions produced by these organisms were observed in the nose, meninges, lungs and cervical and retroperitoneal lymph nodes

and in the spleen, kidneys and adrenal glands. The latter were considerably enlarged, and microscopically there was abundant granulation tissue, with areas of caseation and giant cells containing the doubly contoured spores. The medulla was destroyed, and there was considerable encroachment on the cortex of each gland. Death resulted primarily from the meningeal involvement. The destruction of the adrenal glands was not of sufficient duration to produce symptoms.

Secondary Neoplasms.—A malignant tumor may metastasize to the adrenal glands, but there is usually no evidence of insufficiency. In the histologic examination of such glands numerous nests of functioning adrenal parenchyma are almost constantly present. The following cases are illustrative:

A woman (V. J.), of 55 years, had carcinoma of the breast. Metastases were widespread. Marked weakness during the last year of life kept her confined to bed. The asthenia seemed to be more extreme and more chronic than is ordinarily observed in carcinomatosis and is possibly attributable to destruction of the adrenal glands by the metastatic growths.

A carcinoma of the sigmoid flexure in a man (W. W.), of 62, had metastasized to the mesenteric lymph nodes and both adrenal glands. The symptoms, however, indicated a lesion in the lower part of the intestinal tract. The adrenal glands were large, soft and lobulated; normal adrenal tissue could not be recognized grossly. Histologically, masses of tumor cells were present throughout both glands, which were similar in their morphologic characteristics to the cells in the primary growth. Clusters of cortical cells were preserved in some places.

In a male student (E. R.), of 30 years, very large metastases from a melanoma of the back were observed in the adrenal glands. A pigmented nevus had been excised with difficulty about three years previously and had recurred twice within a year and a half. Numerous secondary growths developed in the skin of the chest and arms and in the axillary lymph nodes. The pronounced weakness, anorexia and emaciation that were present for several months before death may have been due in part to destruction of the adrenal glands. Contrary to the usual picture, the liver contained only a few tiny metastases. Each adrenal gland was replaced by a tumor almost as large as the corresponding kidney. Only small groups of atrophic cortical cells remained, the greater part of the glands being replaced by malignant growth.

CHRONIC ADRENAL HYPERFUNCTION

Hypertrophy.—Simple diffuse hypertrophy of both adrenal glands is infrequent.

Bilateral hypertrophy of moderate degree was observed in a 38 year old woman (L. G. H.), who died of a very malignant adenocarcinoma of the cecum. Hypertrichosis of the face, thighs and legs was the only indication of possible hyperfunction of the adrenal glands. The combined weight of the adrenal glands was 21 Gm.; the measurements were 6.8 by 2 by 1.5 cm. and 5.8 by 4 by 1.2 cm., respectively (fig. 8). Microscopically, the cortex was considerably widened, the greater part consisting of the zona fasciculata. The medulla appeared normal.

Compensatory hypertrophy is more frequently observed. It was first described by Marchand (cited by Goldzieher) and follows the

unilateral destruction or the removal of one adrenal gland. This may be the result of a caseous process or may be due to unilateral aplasia. Experimental compensatory hypertrophy has been produced in albino rats.[17] Removal of one gland is followed by hypertrophy of the remaining one and is practically limited to the cortex.

In a man (H. G.), of 44 years, who died of bilateral bronchopneumonia the autopsy further disclosed hemachromatosis with involvement of the pancreas. Quiescent tuberculous foci were seen in the tracheobronchial lymph nodes. The right adrenal gland was small and consisted almost entirely of a dense yellow homogeneous mass with just visible tiny bits of cortex and medulla. Large, confluent regions of caseation were present microscopically, surrounded by small tubercles and tuberculous granulation tissue. Nests of cortical cells were occasionally seen. The left adrenal gland was about twice the usual size but appeared normal in every other respect. Microscopically, hypertrophy was marked in the cortex and present to a lesser degree in the medulla.

Fig. 8 (L. G. H.).—Diffuse bilateral hypertrophy of the adrenal glands (weight, 21 Gm.).

Cortical Neoplasms.—A cortical adenoma, varying in size from a few millimeters to 1 or 2 cm. is the neoplasm most frequently observed in the adrenal glands. In the majority of cases it gives no clinical evidence of its presence.[7] The frequency of the occurrence of such a small benign growth is borne out by a glance at the table. In none of the cases did the neoplasms produce clinical manifestations; it was observed incidentally at autopsy. Death resulted from arteriosclerotic heart disease in most of these cases. The average size of the adenomas was 1 cm., and the largest one measured 4 by 2 cm. (fig. 9). All the adenomas were composed of cortical cells arranged in a somewhat disorderly fashion.

17. Mackay, E. M., and Mackay, L. L.: Compensatory Hypertrophy of the Adrenal Cortex, J. Exper. Med. **43**:395, 1926.

A malignant growth of the adrenal cortex as a rule has a rapid and fatal course. Such a growth occurs more frequently in women than in men, and changes in the secondary sexual characteristics are often the only signs present, but even these may be absent; this is especially true in men. An addisonian syndrome is very uncommon.

The carcinoma of the adrenal cortex here described occurred in a 53 year old man (B. L.). The large number of infectious diseases in his past history is of some import. He had had typhoid at 12 years of age and rheumatic fever at 16. A gonorrheal infection occurred at 18, with a recurrence at 35 years. Tonsillectomy was done at the age of 46 because of frequent recurrent attacks of tonsillitis and severe cervical arthritis. Eight months before death he first complained of cough, with the production of purulent material and some loss in weight. Roentgeno-

Fig. 9 (C. McM.).—Cortical adenoma of the right adrenal gland. Hypertrichosis of the trunk and upper extremities was the only evidence of possible hyperadrenia.

grams gave evidence of healed apical tuberculosis and a small mass in the mediastinum. Twinges of pain in the left leg, which soon developed into well established radiculitis of the lumbosacral plexus, developed five months before death. A clinical diagnosis of generalized carcinomatosis with metastases to the spine and with pressure on the nerve roots was made. Careful examination failed to reveal the site of the primary growth. Irradiation over the mediastinal region brought about some betterment in the cough but failed to cause any diminution in the tumor. Irradiation over the lumbar part of the spine caused no perceptible improvement. Chordotomy in the upper part of the thoracic region on the right was done two months after the onset of the radiculitis in the hope that it might relieve the patient of his pain. This was accomplished to some extent, but right-sided radiculitis developed one month later. The patient became extremely cachectic and died about eight months after the onset of the clinical symptoms.

At the autopsy the tracheobronchial lymph nodes were enlarged and contained firm gray-white tumor nodules; one of these compressed the right main bronchus. Large nodes in the upper and supero-anterior parts of the mediastinum were adherent to each other and projected into the upper part of the right pleural cavity. The retroperitoneal and inguinal nodes were large and similar to those in the mediastinum and about the lungs. The peritoneum was dotted here and there with tumor nodules; the largest one was in the serosa at the junction of the rectum and the sigmoid flexure. There were nodules in the liver and kidneys. The adrenal glands were at least twice the normal size, and surfaces made by cutting were streaked with gray, firm tumor masses and isolated small islands of yellowish tissue. Microscopically, there were a few islands of cortical cells filled with lipoid. These were surrounded by a tumor composed of columns and small masses of large atypical cells. The latter resembled more or less cells of the

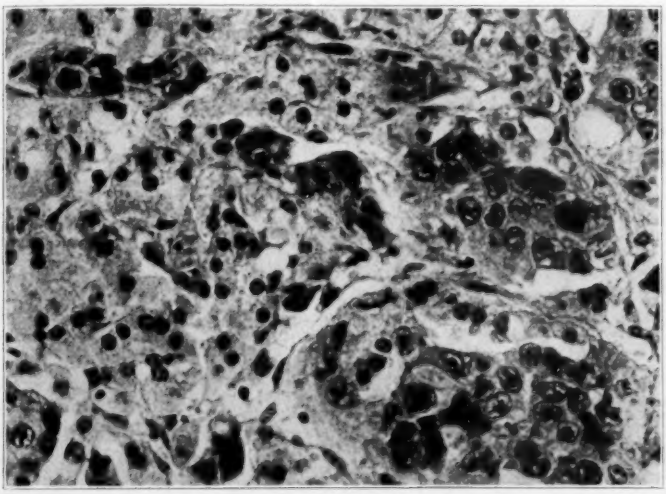

Fig. 10 (B. L.).—Photomicrograph of primary carcinoma of the adrenal glands. The multicentric origin of the tumor is evident, and transitional stages between cortical cells and the tumor may be seen.

adrenal cortex. The tumor cells were supported in places by heavy fibrous stroma and in others by a delicate reticulum. Some of the tumor cells were multinucleated, and others had many mitoses. There was invasion by tumor cells of the capsule and periadrenal fat. In another section the three layers of adrenal cortex were distinguishable, but there were small masses of very large atypical cells in intimate association with the more normal-appearing cells of the adrenal cortex (fig. 10). The blood sinuses were distended, and there were a few small hemorrhages. Small collections of lymphocytes were present in the deeper part of the cortex. The metastatic nodules were similar microscopically to the lesions in the adrenal glands. Terminal bronchopneumonia and fibrinopurulent pericarditis were the only other lesions observed in this body.

Early widespread metastasis and marked cachexia occur frequently in association with adrenal carcinoma. The metastatic lesions often produce the first clinical manifestations of disease.[18] In the case reported here the first symptoms were occasioned by the growths in the tracheobronchial lymph nodes and mediastinum, followed a short time afterward by radiculitis secondary to metastases in the retroperitoneal lymph nodes.

COMMENT

The rather high incidence (12.8 per cent) of adrenal hemorrhage in the adult is noteworthy in this series of 39 records of cases. In 2 persons the hemorrhage was massive and occurred during the course of an acute infectious disease. Clinical signs of adrenal insufficiency were present in only 1 instance (D. F. R.). In 2 other cases hemorrhage of moderate degree occurred in the adrenal glands as a terminal complication (in a case of carcinoma of the prostate and in 1 of myelogenous leukemia). Routine examination of the adrenal glands at postmortem examination has in recent years increased the number of recorded cases of adrenal hemorrhage in the adult.

There is liability to sudden death, spontaneous or postoperative, in chronic adrenal insufficiency. Death may be sudden and unforeseen, as in the case of P. C. T., but is most likely to happen when there is a sudden demand for increased adrenal function. This is well illustrated in 5 cases (those of M. C., J. S., M. L., T. M. and A. H.). It is probable that life could have been prolonged in 4 of these (those of M. C., M. L., T. M. and A. H.) if the operation had been deferred or modified. In each of these patients there were signs and symptoms suggestive of chronic adrenal dysfunction. It is evident from an analysis of these records that there is need of additional criteria in establishing the presence of adrenal lesions in the living patient. Not infrequently hypotension or other signs which the physician associates with hypoadrenia may be found during the course of a physical examination in persons who come to the physician with some ailment requiring surgical intervention. Careful investigation of this group of patients, the idea of adrenal insufficiency being kept in mind, may elicit additional corroborative data. Repeated blood pressure readings are also suggested. If operation becomes imperative it would be well for the surgeon to acquaint the relatives of the possibility of an unfortunate outcome.

Injections of extract of adrenal cortex, accompanied by the oral administration of a sodium salt, have a beneficial effect in Addison's disease. Response to such measures, and frequent blood pressure readings, may aid in the diagnosis in cases in which the symptoms are indefinite and pigmentation is absent.

18. Meyer, J., and Frumess, G.: Tumors of the Suprarenal Gland with Special Reference to Carcinoma of the Cortex, Arch. Int. Med. **48**:611 (Oct.) 1931.

THE ETIOLOGIC SIGNIFICANCE OF STREPTOCOCCI IN EPIDEMIC ENCEPHALITIS

II. EXPERIMENTS WITH ANIMALS AND CONCLUSIONS

KENNETH L. BURDON, Ph.D.

ERIC W. THURSTON, M.D.

PHILIP L. VARNEY, Ph.D.

AND

J. BRONFENBRENNER, Ph.D., D.P.H.

ST. LOUIS

In a previous paper [1] we described the biologic properties of the streptococci obtained from patients with encephalitis, their agglutination reactions with Rosenow's encephalitis antistreptococcus serum and their cataphoretic velocity and compared these data with those obtained by a parallel study of similar cultures from normal persons residing in St. Louis, as well as in a locality far removed from the area of the epidemic. It is the purpose of this communication to describe the results which followed intracerebral inoculation of the cultures obtained from patients and from normal persons into animals and our experiments bearing on the immunologic relationship of the streptococci isolated to clinical encephalitis.

TECHNIC

As in the previously reported work we were at particular pains in the experiments with animals to follow in all essential details the procedures used by Dr. Rosenow, who was kind enough to give us a full personal demonstration. Dr. Rosenow in our laboratory inoculated four rabbits with a strain of Streptococcus which he had freshly isolated from a patient with encephalitis in St. Louis. The following day he performed autopsies on the two rabbits that had died. He later observed rabbits inoculated by us and gave us further advice on dosage and other details.

From the Department of Bacteriology, Immunology, and Public Health, Washington University Medical School.

1. Burdon, K. L.; Thurston, E. W.; Varney, P. L., and Bronfenbrenner, J.: The Etiologic Significance of Streptococci in Epidemic Encephalitis: I. Incidence of Streptococci in Cultures from Patients with Encephalitis in St. Louis and from Normal Controls, and Characteristics of the Various Strains Isolated, Arch. Int. Med. **58**:285 (Aug.) 1936.

The procedures followed in our work with animals are outlined in the following paragraphs:

Inoculation of Animals.—The primary brain broth cultures were inoculated intracerebrally into rabbits in doses of from 0.1 to 0.2 cc. of a 1:10, 1:100 or 1:1,000 dilution of the eighteen to twenty-four hour old culture in broth. In the majority of cases only the smallest dose (0.1 cc. of the 1:1,000 dilution) was used. Pure cultures of the streptococci were inoculated in a dilution of 1:1,000 in all experiments. Albino rabbits were used almost exclusively, ranging in weight from approximately 1,500 to 2,500 Gm. Before inoculation the animals were anesthetized; the hair over the head was clipped, and the exposed surface was thoroughly disinfected with acetone. An incision about 1 inch (2.5 cm.) in length was made in the sterilized area of the skin at about the midline; the skin was held apart, exposing the skull, and was moved a little to the left of the median line. There, at the level of the posterior angle of the eyes, a hole was drilled through the skull by means of a fine steel point, which was equipped with a guard preventing it from penetrating beyond a depth of ⅛ inch (0.3 cm.). The inoculating needle was inserted through this opening and into the brain to a depth of about ⅜ inch (0.9 cm.), withdrawn gradually as the material was injected and finally removed slowly, so as to avoid any loss of the inoculum. The incised skin was brought together and sealed with collodion. Care was exercised to maintain the uniformity of this procedure throughout all experiments. As a check on the nature of the actual material inoculated, a portion of the inoculum was always streaked on blood agar plates immediately after the injection.

Symptoms and Postmortem Observations.—Inoculated animals were watched carefully and frequently were removed from their cages for closer observation and recording of symptoms. In some instances they were photographed by a moving picture camera, and in this manner a permanent record of their behavior in various stages of illness was secured.

Autopsies were performed as soon as possible after death. The entire body of the rabbit was first wet with dilute disinfectant. The skull was opened aseptically, and cultures were made from the ventricular fluid and the brain substance, the material being secured by means of sterile capillary pipets and inoculated directly into tubes of warm dextrose-brain broth and streaked over warm blood agar plates. Usually a direct smear was made from the meninges at the base of the brain or from the spinal fluid in order to determine the character of the exudate if any was present. The chest was then immediately opened, and through the seared surface of the heart from 0.2 to 0.5 cc. of blood was obtained and inoculated into warmed dextrose-brain broth and onto blood agar plates. The brain, medulla and cervical portion of the cord as well as the other principal organs were examined for gross changes; then pieces of tissue from them were fixed in Zenker's acetic acid fixative, and in some instances additional pieces were fixed in formaldehyde. Sections from the tissues prepared with Zenker's fixative were stained by hematoxylin and eosin for study of the microscopic lesions, and the formaldehyde-fixed sections were stained by a modified Gram stain for the demonstration of bacteria.

The cultures in dextrose-brain broth inoculated with the material from the brain were transferred within twelve hours to new (warmed) tubes of the same medium and were maintained thereafter, so long as they were under study, by frequent transplants in the brain broth (from three to six transfers each twenty-four hours). These transfers were always made by removing with a

pipet a portion of the growth from the bottom of the column of broth near the brain substance and depositing this in a similar place near the brain material in the new tube, as recommended by Rosenow.

RESULTS OF INOCULATION OF ANIMALS WITH CULTURES OF STREPTOCOCCI FROM PATIENTS WITH ENCEPHALITIS SELECTED AS TYPICAL BY DR. ROSENOW

Rabbits Inoculated in Our Laboratory by Dr. Rosenow.—Four animals (two albino and two black and tan) were inoculated by Dr. Rosenow personally in our laboratory.

The inoculum used by Dr. Rosenow was a passage strain of green colony streptococci cultured by him on the previous day from the brain of a rabbit which had died after intracerebral injection of the primary dextrose-brain broth culture of material from the nasopharynx of a patient in St. Louis with acute encephalitis. One albino and one black and tan rabbit were inoculated intracerebrally with a growth of this strain in dextrose-brain broth approximately eighteen hours old, representing the second culture in the medium, and the other pair of rabbits (one albino and one black and tan) were inoculated in an identical manner with a younger growth (about ten hours old) of the same strain in its third transfer in the brain medium. In each case the inoculum consisted of 0.1 cc. of a 1:1,000 dilution of the broth culture.

Clinical Symptoms.—Within six hours both albino rabbits exhibited marked respiratory embarrassment and weakness of the limbs, especially the forelegs. They crouched in their cages with the ears back, breathing rapidly and noisily, and each labored breath was accompanied by trembling of the head and the forepart of the body. The rabbit which had received the younger culture showed the more severe symptoms at that time. In twelve hours this animal lay prone in the cage, breathing rapidly, with a gasping or grunting sound which could be heard across the room. When placed on its feet outside the cage, it could maintain its balance with difficulty and would not move unless prodded. It then staggered a few feet only and always in a circle toward the left ("cerebellar gait" [2]). The legs showed marked weakness, especially the forelegs, which tended to spread apart. The head bobbed up and down and weaved about, back and forth ("choreiform movements" [2]). It died approximately twenty hours after inoculation.

The other albino rabbit did not show acute illness quite as rapidly, and twelve hours after the inoculation it was still able to move about, though it was obviously weak and showed gradually increasing difficulty in respiration. At the expiration of twenty-one hours it lay on its side, breathing with marked effort, too weak to do more than raise its head momentarily. While being watched it suddenly went into repeated convulsions and died in about fifteen minutes. At death the body was in rigid extension, with the hindlegs stretched backward and the head retracted.

As had been predicted by Dr. Rosenow, the two black and tan rabbits inoculated at the same time and with the same material as the albino rabbits proved

2. The terms "cerebellar gait" and "choreiform movements" were suggested by Dr. Rosenow as appropriate in describing the symptoms exhibited by this rabbit and when used in this paper they refer to the behavior described here.

to be distinctly more resistant than the latter. The animal receiving the eighteen hour old culture showed no definite symptoms for twenty-four hours. At that time there were present a slight unsteadiness in walking, a reluctance to move and a slight trembling of the forepart of the body. During the second day these symptoms became somewhat more pronounced, and, in addition, there was present a marked edema of the eyes and lacrimation. Respiration was somewhat rapid and irregular but not particularly labored. This condition continued practically unchanged until the third day, when convulsions suddenly developed and the rabbit died, fifty-one hours after the inoculation.

The other black and tan rabbit likewise did not appear definitely ill until about twenty-four hours after the inoculation and at first showed only a slight ataxia, trembling and edema of the eyes. Very severe convulsions soon occurred, however, following one another rapidly, while in the brief intervals between the animal lay on its side with the head and neck extended, gasping for breath. These convulsions continued at intervals of a few minutes for about two hours; then during the next five hours they became gradually less frequent and less severe, and eventually the animal was able to regain its feet after each seizure. The head was in almost continuous motion, weaving back and forth, but occasionally it came to rest sharply retracted, so that it was almost perpendicular to the neck. The eyes showed extreme edema. During the next three days the conjunctivae became opaque and there was marked nystagmus, but otherwise the general condition of the animal gradually improved. Convulsions still occurred occasionally but were less violent, and for considerable intervals the rabbit sat quiet, although the slightest stimulus, such as a sudden noise made by clapping of the hands, would cause the choreiform movements of the head to begin over again. A week after the inoculation the animal had a normal appetite; the eyes had returned to a normal condition, and the generalized convulsions no longer occurred. A mild degree of ataxia and the peculiar movements of the head with occasional sharp retraction or drooping continued, however, and this abnormal behavior persisted during the succeeding seven months during which the animal was observed [3] (fig. 1 *A*).

The symptoms elicited in the albino rabbits as described were regarded by Dr. Rosenow as demonstrating the typical effects of "encephalitis" streptococci. Soon after the death of these rabbits autopsies were performed by Dr. Rosenow, and the notes on the gross changes observed at the time are given here. Additional comments made by Dr. Rosenow are indicated in parentheses.

Autopsy reports on the rabbits follow.

RABBIT 374.—(Albino rabbit inoculated with the ten hour old culture of Rosenow's strain 302 in its third transfer.)

3. The relatively greater resistance of black and tan rabbits over the albino rabbits noted in this experiment seems to be real and not accidental, since we observed it again when we purposely inoculated one rabbit of each kind with the identical dose of a primary culture from the nasopharynx. The albino rabbit died in less than twenty-four hours, while the black and tan rabbit survived, though mild ataxia and peculiar choreiform movements of the head persisted for more than two months thereafter.

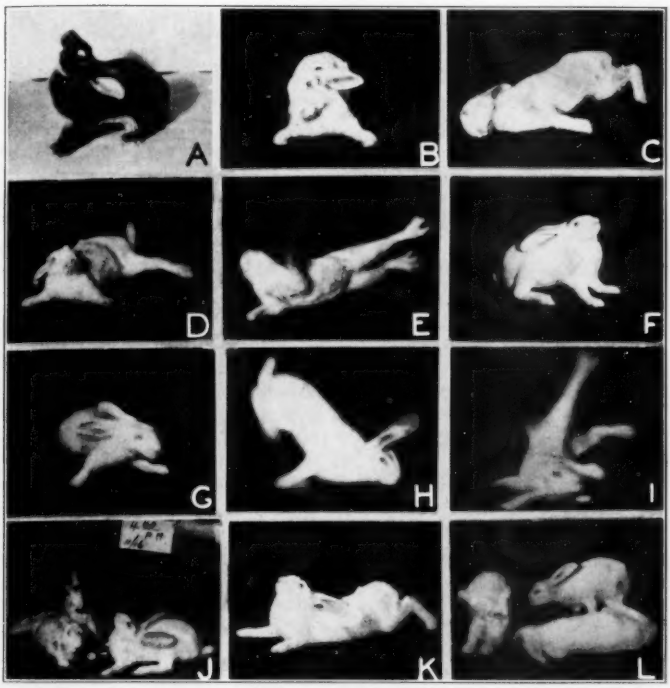

Fig. 1.—*A*, black and tan rabbit inoculated in our laboratory by Dr. Rosenow with a pure culture of streptococci isolated by him on the previous day from the brain of a rabbit which had died after intracerebral injection of the primary nasopharyngeal culture from a patient with encephalitis in St. Louis, showing the position often assumed by the animal during the acute illness and at intervals for many weeks after the inoculation. *B*, early stage of illness (about sixteen hours after inoculation) in a rabbit inoculated with a pure culture of green colony streptococci (passage strain En 24) isolated by us from a patient with encephalitis. *C*, same rabbit as in *B*, shortly before death. *D*, a rabbit inoculated with a pure culture of streptococci (passage strain En 29) originating from a patient with encephalitis, about twenty-four hours after the inoculation. *E*, same rabbit as *D*, showing convulsive movement in late stage of the illness. *F*, *G*, *H* and *I*, progressive stages of illness in a rabbit receiving intracerebrally a mixture of a pure culture of streptococci (passage strain En 29) and human encephalitic convalescent serum (note the similarity to those rabbits [*D* and *E*] receiving the culture alone). *J*, three of the rabbits used in a protection experiment, photographed about twenty-four hours after the inoculations; the animals (left to right) received, respectively, a mixture of a culture of streptococci (passage strain En 29) and normal horse serum, the same culture alone and the same culture mixed with human encephalitis convalescent serum. *K*, opisthotonos in a rabbit injected with a mixture of a streptococcus culture (passage strain En 29) and Rosenow's encephalitis antistreptococcus serum, photographed fifty hours after inoculation. *L*, a group of rabbits in a protection experiment twenty-four hours after inoculation; the animal at the left received a mixture of a pure streptococcus culture (passage strain En 29) and human encephalitis convalescent serum; the animal in the foreground received the same culture alone; the animal in the rear received this culture mixed with Rosenow's encephalitis antistreptococcus serum (the latter rabbit shows practically no symptoms). All photographs are enlargements from a motion picture film.

External Appearance: The animal was in rigid extension. Little rigor mortis was present (common finding). Extreme congestion of the veins of the ear was present.

Eyes: Extreme edema of the conjunctivae was present, and there were several petechiae in the circumcorneal areas. (The changes of the eyes probably are the counterpart of those responsible for ocular symptoms in human patients with encephalitis.)

Brain: Slight cloudiness of the meninges and of the cerebrospinal fluid was noted (in this case there was more gross meningitis than is usually seen in inoculated rabbits). A small hemorrhage was present at the site of inoculation only. (No abscess is ever seen at the site of inoculation.) No petechiae or pink tinge was observed in the arachnoid. The brain showed only a moderate degree of softening and congestion of the cerebral vessels.

Thoracic Organs: The trachea was congested and hemorrhagic, especially in the lower half. The lungs showed marked hemorrhagic edema of all the lobes. (The lesions of the lungs and the trachea were almost identical with those seen in rabbits dying after intracerebral injection of "influenza" strains of streptococci.) The heart showed extreme contraction of the left ventricle (often noted). Numerous subepicardial petechiae were present over both the right and the left ventricle, and subendocardial hemorrhages were noted, several extending into the base of the valves. The myocardium showed marked cloudy swelling and appeared cyanotic and gray. (These changes are not seen in rabbits dying after injection of "poliomyelitis" strains of streptococci.)

Abdominal Organs: The spleen was slightly softened; the liver showed marked cloudy swelling and the kidneys showed swelling, with moderate edema and congestion and slight cyanosis.

Rabbit 378.—(Albino rabbit inoculated with the eighteen hour old culture of Rosenow's strain 302 in its second transfer.)

External Appearance: The forelimbs and hindlimbs were fully extended, some stiffness of the back was noted. The veins of the ear were markedly dilated.

Eyes: The conjunctivae were edematous. Subconjunctival circumcorneal petechiae were present in the left eye.

Brain: The meninges were smooth and shining, without any cloudiness. There was a slight increase in the amount of spinal fluid. Moderate congestion was present in the vessels of the medulla and of the anterior lobes, but there were no petechiae. No lesion was noted at the site of inoculation.

Thoracic Organs: The trachea was markedly congested and hemorrhagic. Several subpleural hemorrhages were noted in both the right and the left lung, with no change in the pulmonary tissue proper. The heart showed much less congestion of the pericardial vessels than usual. Several subepicardial petechiae were present over the left ventricle, and there were numerous subendocardial petechiae in both ventricles, some extending into the valves. (These lesions were less severe than those observed in rabbits previously inoculated by Rosenow with cultures from patients in St. Louis.)

Abdominal Organs: The spleen was swollen, soft and cyanotic (acute splenitis). The adrenal glands were normal (they almost never show gross changes). Cloudy swelling was present in the liver. The kidneys were slightly cyanotic (mulberry color) and swollen; the cortex was gray. The markings were conspicuous, and there was a marked congestion at the corticomedullary junction. (Changes in the kidneys may be due to toxin or may be secondary to pulmonary lesions; in this case the lungs were normal. The mulberry color

of the kidney is very typical and seems to be a change peculiar to and characteristic of the disease produced in rabbits by the St. Louis strains of the encephalitis streptococcus.[4])

Pathologic Changes in the Brain: Sections of the brain tissue from one of these albino rabbits and from the black and tan rabbit that died as well as from two other albino rabbits inoculated by Dr. Rosenow elsewhere in St. Louis with cultures from patients with encephalitis were available to us for microscopic study. In the sections from each of the four animals there was noted an infiltration of the pia-arachnoid by a mixture of polymorphonuclear leukocytes and large lymphocytes (fig. 2 *A* and *C*). In three of these instances an exudate containing mostly polymorphonuclear cells was present in the ventricular cavities. The vessels of the arachnoid were dilated, and occasionally small hemorrhages were seen. In two instances the peripheral vessels—those arising in the pia-arachnoid and extending into the subjacent brain tissue—were surrounded by cuffs consisting of both polymorphonuclear leukocytes and large lymphocytes (fig. 2 *A* and *D*). Cells of the same kind were also seen diffusely scattered in the upper layers of the cortex and in the subependymal tissue. Perivascular cuffing with round cells only, so characteristic of the lesions of encephalitis in human patients,[5] was not observed, and such perivascular infiltration as was noted appeared only in the superficial layers of the brain. Changes in the nerve elements, such as chromatolysis, loss of Nissl bodies and neuronophagy, were not observed. In brief, the main changes were those of purulent meningitis. Diplostreptococci were stained in the pia-arachnoid in three cases and also in one case in the superficial layers of the subependymal tissue near areas in which the continuity of the ependymal lining had been interrupted (fig. 2 *E*).

Rabbits Inoculated by Us with Strains of Encephalitis Streptococci Isolated by Dr. Rosenow.—Further data on the type of symptoms and pathologic changes to be expected in rabbits inoculated with green colony streptococci from patients with encephalitis were secured by us when we later inoculated fourteen other albino rabbits with two different strains of encephalitis streptococci sent to us from Rochester by Dr. Rosenow. Both strains had been isolated by him shortly before from the throats of patients with encephalitis in St. Louis. One of them (strain no. 7777 [3] R7436 Br), which we designated Ros. 2, represented the third animal passage of that strain, and the other (strain no. 8231 [2] R7424 Br), which we designated Ros. 3, was in its second animal passage when received by us.

The strain Ros. 2 was at once passed through two rabbits in succession, thus taking it through the fifth animal passage. The strain Ros. 3 was carried through five consecutive passages, the final inoculation thus representing the

4. Later, after he had had further opportunity to observe rabbits inoculated with material from patients in St. Louis, Dr. Rosenow informed us in personal conversation that he had not found the changes of the kidneys so constant or so characteristic as he had at first believed them to be.

5. McCordock, H. A.; Collier, W., and Gray, S. H.: The Pathologic Changes of the St. Louis Type of Acute Encephalitis, J. A. M. A. **103**:822 (Sept. 15) 1934.

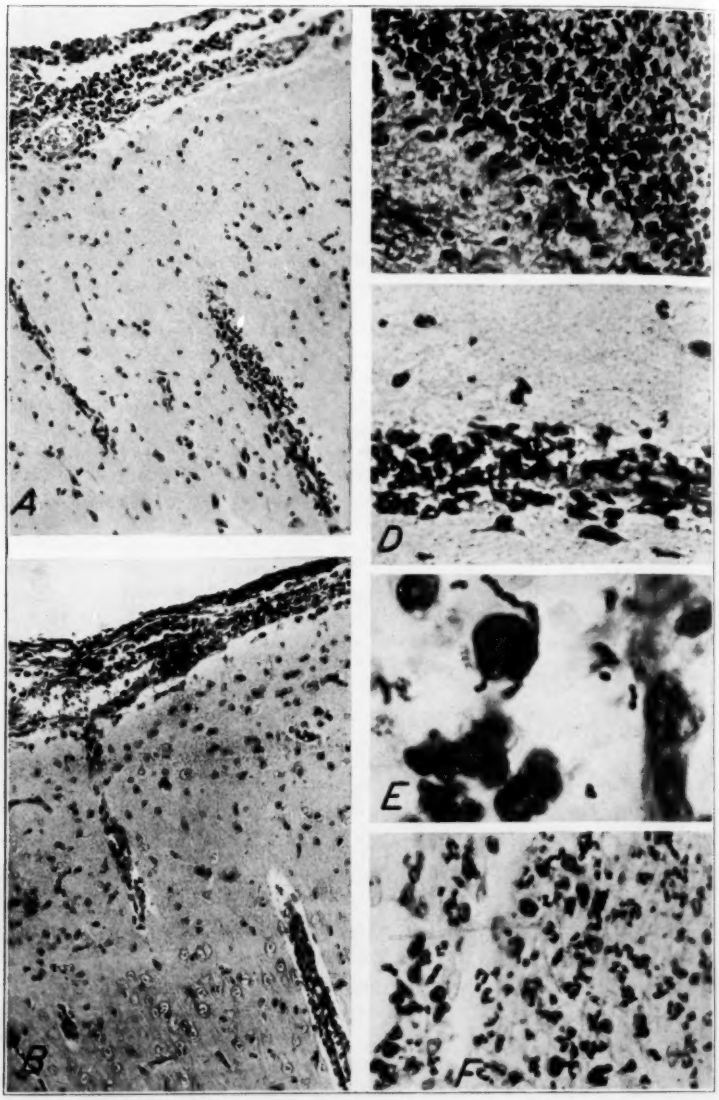

Fig. 2.—*A*, section of the cerebral cortex of an albino rabbit inoculated in our laboratory by Dr. Rosenow with a culture of green colony streptococci isolated by him from a patient with encephalitis in St. Louis. *B*, a section of the cerebral cortex of a rabbit inoculated by us with a pure culture of streptococci isolated from a patient with encephalitis (note infiltration with polymorphonuclear and mononuclear cells in the meninges and the parenchyma, and about the superficial vessels, as in *A*). *C*, purulent meningeal exudate in a rabbit inoculated with one of Rosenow's strains of "encephalitis streptococci." *D*, enlargement to show the character of the perivascular infiltration in *A*. *E*, exudate in the ventricular cavity of an inoculated rabbit, showing the streptococci. *F*, purulent exudate in the meninges of a rabbit inoculated by us with the primary culture from the nasopharynx of a patient acutely ill with encephalitis.

seventh animal passage for this strain. A total of twelve rabbits were inoculated with the strain Ros. 3, groups of several animals receiving the identical culture at the same time. This was done in order to ascertain to what extent the progress of the infection may vary in individual rabbits inoculated with the same material. All the animals—those inoculated with strain Ros. 2, as well as those receiving the Ros 3 strain—died, the majority in less than twenty-four hours.

The symptoms in all these rabbits were fairly uniform and similar to those observed in the two albino rabbits inoculated by Dr. Rosenow, already described. The percentage incidence of the principal symptoms in all the sixteen albino rabbits inoculated with Rosenow's strains is given in table 1.

The first signs of illness were apparent in most of the animals within from eight to ten hours after the inoculation. In a few cases the early symptoms of mild ataxia, reluctance to move voluntarily and moderate dyspnea persisted without any apparent advance in severity for ten or twelve hours before acute illness developed, but usually the symptoms became progressively more grave from their first appearance until death. It could not be said that the animals were lethargic at any time. On the contrary, in the early stages of the illness they were unusually excitable. Choreiform movements of the head were always observed early, and in the majority of instances the head when at rest became more and more strongly retracted. The neck and head were often twisted sharply to the right or left. Exceptionally the head dropped forward and came to rest continuously on the floor. About half the rabbits acquired a marked edema of the circumconjunctival tissues; a smaller proportion showed nystagmus.

One of the first signs noted was the weakness of the legs, which tended to buckle under when the weight was on them. Usually the forelegs eventually spread wide apart, and the animal was unable to hold them together despite all effort to do so. The hindlegs, on the contrary, were not greatly weakened and rarely became paralyzed. At the time when the symptoms were well developed, the rabbits appeared dazed and disoriented and if prodded would stagger dizzily in a circular path, turning always in the same direction. Later the animals fell on the side, and while at first they were able to regain a sitting position by violent effort, they could not maintain it and eventually they could no longer rise at all. In all the rabbits gross tremors of various muscles all over the body were observed. Generalized convulsions were not the rule, but in the final stage more than half the rabbits had involuntary spasmodic movements of large groups of muscles, which we often reported as convulsions. About a third of the animals collapsed on the side rather early in the course of the illness and remained thus for a protracted period before death, during which time there was observed a very slow sinking of their vitality.

In the majority of the rabbits severe dyspnea existed throughout the illness, and there usually developed a purulent discharge from the nose in which gram-positive diplococci were demonstrable microscopically. In the few animals in which the respiratory embarrassment was relatively slight, the symptoms were less acute, and in general the degree of involvement of the respiratory system was apparently more closely correlated with the severity of the illness and the time of death than with any other factor.

It is to be especially noted that, although the illness in all the rabbits followed a fairly uniform and to a certain degree predictable course, there was considerable variation in the prominence with which different symptoms, such as the tremors of the body, movements of the head or abnormal postures, developed in different rabbits, and these variations were as marked among the individual animals in the

TABLE 1.—*Incidence of Symptoms and Mortality in Rabbits Inoculated Intracerebrally with Cultures Containing Green Colony Streptococci from Patients with Encephalitis and from Normal Persons in St. Louis and Washington, D. C.*

Inoculum	Total Number of Strains	Total Number of Albino Rabbits Inoculated		Number and Percentage of Rabbits Showing Particular Symptoms: Ataxia; Cerebral Gait	Dyspnea	Choreiform Movements of Head	Drooping of Head	Retracted Head	Head Twisted to One Side	Edema of Eyes	Nystagmus	Forelegs Weakened, Spread Apart	Hindlegs Paralyzed	Legs Extended at Death	Tremors of Body	Convulsions	Protracted Collapse Before Death	No Symptoms	Symptoms, with Recovery	Mortality: Total	Mortality: Percentage of Total Number Inoculated	Mortality: Percentage Dying in 48 Hours or Less	Green Colony Streptococci Recovered at Autopsy: From Brain: Pure	From Brain: Mixed	From Heart Blood: Pure	From Heart Blood: Mixed
Pure cultures of encephalitis streptococci isolated by Rosenow	3	16	Total observed.....	12	13	12	16	16	16	14	12	13	12	16	11	11	16	..	..	..	..	..	10	10	9	9
			No. showing symptom	12	13	12	2	11	7	6	2	13	1	12	11	6	5	0	0	16	100	75	10	0	5	0
			Percentage incidence..	100	100	100	12	69	44	43	17	100	8	75	100	54	31	..	..	..	..	..	100	0	56	0
Unpurified primary cultures from the nasopharynges of patients with encephalitis in St. Louis	21	23	Total observed.....	15	18	14	19	19	19	12	12	16	19	18	14	14	18	..	..	..	..	..	15	15	14	14
			No. showing symptom	15	18	14	6	15	9	8	2	16	2	15	12	2	10	4	1	18	78	72	7	5	3	0
			Percentage incidence..	100	100	100	32	79	47	67	17	100	10	83	86	14	66	..	..	..	..	..	47	33	21	0
Pure cultures of streptococci isolated by us from patients in St. Louis	3	31	Total observed.....	28	29	25	31	31	31	29	28	28	28	30	27	25	31	..	..	..	..	..	15	15	5	5
			No. showing symptom	28	29	24	10	28	15	19	4	28	10	20	27	4	4	0	0	31	100	84	15	0	2	0
			Percentage incidence..	100	100	96	32	90	48	65	14	100	36	67	100	16	13	..	..	..	..	..	100	0	40	0
Totals	27	70	Total observed.....	55	60	51	66	66	66	55	52	57	59	64	52	50	65									
			No. showing symptom	55	60	50	18	54	31	33	8	57	13	47	50	12	19	4	1	65	93	77				
			Percentage incidence..	100	100	98	27	82	47	60	15	100	22	73	96	24	29									
Unpurified primary cultures from the nasopharynges of normal persons in St. Louis	4	4	Total observed.....	3	3	2	3	3	3	2	2	3	3	3	1	1	3	..	..	..	..	..	3	3	3	3
			No. showing symptom	3	3	2	2	1	0	1	0	3	2	1	1	1	1	1	0	3	75	100	2	1	0	1
			Percentage incidence..	100	100	100	67	33	0	50	0	100	67	33	100	100	33	..	..	..	..	..	67	33	0	33
Unpurified primary cultures from the nasopharynges of normal persons in Washington, D. C.	6	6	Total observed.....	6	6	6	6	6	6	6	6	6	6	4	6	6	4	..	..	..	..	..	4	4	4	4
			No. showing symptom	6	5	6	1	2	5	2	1	6	2	2	5	1	1	0	0	4	67	75	2	1	1	1
			Percentage incidence..	100	83	100	17	33	83	33	17	100	33	50	83	17	25	..	..	..	..	..	50	25	25	25
Pure cultures of streptococci isolated by us from normal persons in St. Louis and Washington, D. C.	6	6	Total observed.....	2	2	2	4	4	4	2	2	3	4	3	2	2	3	..	..	..	..	..	2	2	2	2
			No. showing symptom	2	1	2	1	3	0	0	0	3	0	3	2	0	0	2	1	3	50	66	2	0	1	0
			Percentage incidence..	100	50	100	25	75	0	0	0	100	0	100	100	0	0	..	..	..	..	..	100	0	50	0
Totals	16	16	Total observed.....	11	11	10	13	13	13	10	10	12	13	10	9	9	10									
			No. showing symptom	11	9	10	4	6	5	3	1	12	4	6	8	2	2	3	3	10	62	81				
			Percentage incidence..	100	82	100	31	46	38	30	10	100	31	60	89	22	20									

groups of rabbits receiving the identical culture at the same time as they were among the rabbits receiving comparable doses of different strains.

At the autopsy of ten of these sixteen animals cultures were made from the brain. In all instances the culture yielded a pure growth of streptococci, as did also the cultures of blood from five of nine of the rabbits.

The pathologic changes observed in the rabbits inoculated with strain Ros. 2 and Ros. 3 did not differ materially from those in the animals inoculated by Dr. Rosenow and described previously. In table 2 the percentage incidence of the principal pathologic findings in all the sixteen rabbits inoculated with Rosenow's cultures is given.

Grossly, more than two thirds of the animals showed a marked engorgement of the vessels of the leptomeninges, especially about the base of the brain. In two instances the cortex had a definitely pinkish tinge. There was present a visible meningeal exudate in three instances (19 per cent). Small subarachnoid hemorrhages were present in about a third of the rabbits, and in about half of them there occurred hemorrhage into the brain substance. The latter, however, consisted merely of small petechiae about the site of injection, except in three instances in which apparently fresh hemorrhages of considerable size had occurred. Petechiae in the heart and in the pleura were each observed in about one fourth of the animals. Sixty-nine per cent of the rabbits showed hemorrhagic edema of some degree in the lungs. Slight congestion of the liver was noted in a few cases, and in the majority the spleen was found to be moderately swollen and softened. The kidneys were congested in some degree in all the animals, but there was nothing peculiar or characteristic about the appearance of these organs.

Microscopic examination of the brains of the rabbits of this group revealed essentially the same picture as was seen in the animals inoculated by Rosenow and described earlier. The majority of the rabbits showed the presence of a meningeal exudate as the most conspicuous feature. This exudate always consisted of a mixture of large lymphocytes and polymorphonuclear cells, which were present in various proportions in different parts of the same sections. Infiltrations of lymphocytes and polymorphonuclears were also observed about the superficial cortical vessels, but perivascular cuffing with round cells alone was not seen. No changes in the nerve cells were observed. The streptococci were readily demonstrable in the meningeal exudate and occasionally in the cortical parenchyma.

Monkeys Inoculated with One of Rosenow's Strains.—Since in the early study of this epidemic the transmissibility of encephalitis to monkeys by intracerebral inoculation with a filtrable virus from the brains of patients with encephalitis had been established, it was deemed interesting to compare the symptoms and pathologic changes observed in these animals as the result of injection of the virus with those which might be produced by injection of the streptococci.

The relative insusceptibility of rhesus monkeys to intracerebral inoculation with green colony streptococci has been noted by several authors. Rosenow in his attempts to infect monkeys with his strains of streptococci isolated from patients with poliomyelitis and encephalitis usually adopted the procedure of giving repeated intracerebral inoculations (three or more) at intervals of a few days until some sort of symptoms were produced.

TABLE 2.—*Gross and Microscopic Pathologic Changes in Rabbits Inoculated Intracerebrally with Cultures Containing Green Colony Streptococci from Patients with Encephalitis and from Normal Persons in St. Louis and in Washington, D. C.*

Inoculum	Total Number of Autopsies		Number and Percentage of Rabbits Showing Particular Pathologic Changes																						
			Gross Pathologic Findings													Microscopic Pathologic Observations									
			Brain					Eyes		Heart	Lungs	Liver	Spleen	Kidneys		Brain					Lungs		Liver	Kidneys	
			Cortical Vessels Engorged	Meningeal Exudate	Hemorrhage in Brain Substance	Subarachnoid Hemorrhage	Pinkness of Cortex	Circumcorneal Congestion or Hemorrhage	Conjunctival Edema	Subcardial, Epicardial or Endocardial Hemorrhages	Hemorrhagic Edema	Subpleural Hemorrhages	Congestion	Swelling, Softening	Congestion	Purulent Meningitis	Hemorrhages in Parenchyma	Perivascular Infiltration	Bacteria: In Exudate	Bacteria: In Parenchyma	Edema	Bronchopneumonia	Cloudy Swelling	Cloudy Swelling
Pure cultures of encephalitis streptococci isolated by Rosenow	16	Total observed	16	16	16	16	16	10	10	13	13	13	13	13	13	5	5	5	5	5	1	1	1	1	
		No. showing positive changes	13	3	9	6	2	2	3	3	9	3	2	10	13	4	1	3	5	2	0	0	1	1	
		Percentage incidence	81	19	56	37	12	20	30	23	69	23	15	77	100	80	20	60	100	40	0	0	100	100	
Unpurified primary cultures from the nasopharynges of patients with encephalitis in St. Louis	15	Total observed	15	15	15	15	15	5	8	15	15	15	15	15	15	13	13	13	13	13	9	9	9	10	
		No. showing positive changes	11	1	8	3	2	0	3	5	6	4	6	8	7	13	1	7	10	3	5	1	5	7	
		Percentage incidence	73	7	53	20	13	0	37	33	40	27	40	53	47	100	8	54	77	23	55	11	55	70	
Pure cultures of streptococci isolated by us from patients in St. Louis	31	Total observed	31	31	31	31	31	23	24	31	31	31	31	31	31	7	7	7	6	6	3	3	5	5	
		No. showing positive changes	22	9	10	5	6	4	2	3	13	6	14	9	23	7	2	6	6	2	2	0	2	2	
		Percentage incidence	71	29	32	16	19	17	8	10	42	19	45	29	74	100	28	85	100	33	67	0	40	40	
Totals	62	Total observed	62	62	62	62	62	38	42	59	59	59	59	59	59	25	25	25	24	24	13	13	15	15	
		No. showing positive changes	46	13	27	14	10	6	8	11	28	13	22	27	43	24	4	16	21	7	7	1	8	10	
		Percentage incidence	74	21	43	23	16	13	19	19	47	22	37	46	73	96	16	64	87	29	54	8	53	67	
Unpurified primary cultures from the nasopharynges of normal persons in St. Louis and in Washington, D. C.	7	Total observed	7	7	4	7	7	2	2	7	7	7	7	7	7	3	3	2	3	3	0	0	0	0	
		No. showing positive changes	7	3	0	0	0	1	1	0	5	1	2	6	6	3	1	2	3	3					
		Percentage incidence	100	43	0	0	0	50	50	0	71	14	28	86	86	100	33	100	100	100					
Pure cultures of streptococci isolated by us from normal persons in St. Louis and in Washington, D. C.	3	Total observed	3	3	3	3	3	0	0	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	
		No. showing positive changes	1	2	1	2	0	..	..	0	1	0	1	2	2										
		Percentage incidence	33	67	33	67	0	0	..	0	50	0	50	100	100										
Totals	10	Total observed	10	10	7	10	10	2	2	9	9	9	9	9	9	3	3	2	3	3	0	0	0	0	
		No. showing positive changes	8	5	1	2	0	1	1	0	6	1	3	8	8	3	1	2	3	3					
		Percentage incidence	80	50	14	20	0	50	50	0	67	11	33	89	89	100	33	100	100	100					

The strain Ros. 3 was chosen for the inoculation of monkeys, since it was the most typical of those available. Not only was this strain capable of producing in rabbits the characteristic illness (as noted), but it was agglutinated in high dilution (1:10,240) by Rosenow's "encephalitis antistreptococcus serum" and subcultures showed frequently an average cataphoretic velocity approaching the "neurotropic" zone (i. e., a cataphoretic time of about 4 seconds). Just prior to the inoculation of the monkeys a culture of this strain was injected intracerebrally in the dose of 0.1 cc. of a 1:1,000 dilution into an albino rabbit (fourth animal passage). This rabbit had the usual illness and died in about forty hours. The streptococci were cultured from the brain in dextrose-brain broth, and this culture, twelve hours old, was injected intracerebrally in the amount of 0.5 cc. of a 1:100 dilution into a normal monkey. No sign of illness of any kind appeared as a result of this inoculation during several weeks in which the monkey was observed.

Two days later a second monkey was inoculated intracerebrally with the same strain, which had been passed in the meantime through many transfers in dextrose-brain broth medium. This monkey was given 1 cc. of the undiluted culture—an extremely heavy inoculation. In order to test the nature of the relatively high resistance of monkeys to streptococci (as noted in the first monkey inoculated) this second monkey was bled just before it was inoculated, and a rabbit was inoculated intracerebrally with a mixture of an equal volume of the monkey's serum and a 1:500 dilution of the same culture. The mixture of the diluted culture and the normal monkey serum was allowed to stand at incubator temperature for one and one-half hours before it was inoculated intracerebrally into the rabbit. Another rabbit was inoculated at the same time with a 1:1,000 dilution of the identical culture (without serum) as a control.

Twelve hours after the inoculation the monkey was definitely ill. It crouched in the corner of the cage with the head down between the shoulders. It was hard to arouse, but a sufficiently sharp noise would cause it to raise the head and take a few steps. When let alone it would return immediately to a crouching attitude, shivering slightly from time to time. Coarse tremors of the forelimbs were occasionally seen. The head was sometimes held sharply retracted for a brief period. The left eye (on the side of inoculation) showed edema and ptosis of the lid. The right showed only a tendency to profuse lacrimation. These abnormalities lasted for only a few hours, however, and within twenty-four hours after the inoculation both eyes appeared normal and all other symptoms had almost disappeared. Before the next day the animal fully recovered, and no residual symptoms of any kind were noted during the following several weeks of observation.

In sharp contrast, the control rabbit receiving the same (though greatly diluted) culture had the usual acute illness and died in about eighteen hours. The rabbit inoculated with the mixture of the culture and monkey serum also showed typical symptoms and collapsed early but lingered in this state, barely alive, for three days. This result suggests that the normal monkey serum may possibly have had some slight protective effect.

RESULT OF INOCULATION OF ANIMALS WITH CULTURES OBTAINED BY US FROM PATIENTS WITH ENCEPHALITIS

Primary Cultures from the Nasopharynx.—The primary dextrose-brain broth cultures from the nasopharynges of twenty-one patients with encephalitis were inoculated into a total of twenty-three albino rabbits.

The material for culture was obtained in the manner previously described and was incubated about eighteen hours, and in no case for more than twenty-eight hours, before inoculation. The dose in all cases was 0.1 cc., intracerebrally, of a freshly made dilution in warm broth. Eight of the animals received the culture in a 1:10 dilution, four in a 1:100 dilution and eleven in a 1:1,000 dilution. Of the twenty-three rabbits thus inoculated, one showed only mild and transient symptoms followed by complete recovery; four showed no symptoms whatever, and eighteen (78 per cent) showed progressive illness and died. Of the eighteen deaths, thirteen (72 per cent) occurred within forty-eight hours after the inoculation and the remaining five in from three to five days (table 1).

The degree of dilution of the primary culture apparently was not the decisive factor in determining the final outcome of infection, since nine of the eleven rabbits receiving the least amount of culture (1:1,000 dilution) died, whereas one of the rabbits receiving a 1:100 dilution had transient symptoms only, and among the four animals which showed no symptoms at all, two received the largest amount (1:10 dilution) of the cultures.

At the time the nasopharyngeal swabbings were made, nineteen of the twenty-one patients were acutely ill and presented clinically typical encephalitis of from two to nine days' duration; one patient had mild and atypical symptoms only of nineteen days' duration, and one was convalescent after a typical attack of acute encephalitis three weeks earlier. No correlation could be made out between the clinical state of the individual patient from whose nasopharynx the cultures were obtained and the character and severity of the symptoms in the inoculated rabbits. The culture from the patient with a mild, atypical attack and also the one from the convalescent patient produced a fatal illness like that caused by other primary cultures from the nasopharynges of the acutely ill. All the four rabbits that showed no symptoms received cultures from patients with typical acute encephalitis.

On the other hand, the results of the inoculation of the rabbits appeared to be definitely influenced by the relative number of green colony streptococci present in the injected material, as revealed by the control streaked blood agar plates made from each inoculum at the time of inoculation. These plates showed that the material injected in all cases was a mixture containing green colony streptococci and a variable proportion of other organisms, mainly staphylococci, except in two instances in which the inoculum consisted of an apparently pure culture of the streptococci. That the green colony streptococci in these cultures were principally responsible for the acute infection and death which occurred in most of the rabbits is clearly indicated by the somewhat milder illness that followed inoculation with certain of the primary cultures in which streptococci were comparatively few, as well as by the fact that cultures from the brains of the rabbits at autopsy yielded in many cases practically a pure growth of these streptococci.

Four animals received cultures in which staphylococci or other bacteria were apparently more numerous than the streptococci. In two of these rabbits the illness ran a slower and milder course than usual, and these two were the only rabbits of the entire group that survived as long as five days. No organisms were recovered from the brain of one of these animals, and from the other an almost pure growth of hemolytic staphylococci, accompanied by only a few colonies of green colony streptococci, was obtained. A third rabbit showed acute symptoms and died in about thirty hours, but in this case a heavy growth of green streptococci, mixed with a smaller number of hemolytic staphylococci, appeared in cultures from the brain. The fourth animal was among those showing no symptoms.

The three other rabbits that remained without symptoms, as well as the animal that had transient illness only, received cultures which contained apparently as many green colony streptococci as did most of the cultures that produced acute disease in other animals. These were among the earlier experiments, however, and it is believed that the failure to cause the usual illness might have been due to the escape of part of the inoculum from the skull after injection.

The predominance of green colony streptococci in the brains of those rabbits that died after intracerebral injection of the unpurified primary cultures from the nasopharynges of the patients with encephalitis was clearly shown in the cultures made at autopsy (table 1). Fifteen rabbits were examined bacteriologically. In three instances cultures from the brain in dextrose-brain broth yielded no growth, but in all the remaining twelve (80 per cent) the cultures from the brain contained green colony streptococci. These were distinctly more abundant than any other organism in nearly every instance, and in the case of seven of the animals (47 per cent) they were the only organisms found. It appears that when the green colony streptococci were sufficiently numerous in the original inoculum they multiplied freely in the brains of the inoculated animals and tended to crowd out the accompanying organisms. In contrast to the regularity of their presence in the brain, the streptococci were observed at autopsy in the blood of only three rabbits of the fourteen examined (21 per cent). These results are in accord with those reported after similar intracerebral inoculations of rabbits with mixed cultures from patients with diseases of the nervous system by Rosenow, and it is findings of this kind which are the basis of Rosenow's contention that these green colony streptococci exhibit neurotropic properties.

The symptoms observed in this group of rabbits receiving inoculations of primary cultures from the nasopharynges of patients with encephalitis closely resembled those in animals inoculated with the cultures of streptococci obtained from Dr. Rosenow, as described earlier. The percentage incidence of the various symptoms was very nearly the same in the two groups of rabbits (table 1). In general, fewer of the animals given the primary cultures were observed in convulsions, a larger proportion died a lingering death after a protracted period of collapse and there was perhaps a somewhat greater variation in the character of symptoms in individual rabbits, but there were no significant or consistent differences in the course of the illness which would distinguish it from that produced by the injection of Rosenow's cultures.

As noted before, severe respiratory symptoms were associated with early death. It was impossible to predict correctly from the symptoms shown by a particular animal whether at autopsy the cultures from the brain would reveal the presence of streptococci only or a mixture of streptococci and other organisms. The prominence of certain symptoms in a particular animal (such as extreme torticollis, retraction of the head, marked nystagmus and edema of the eyes, or spasms of the diaphragm) could not be correlated in any case with the clinical history of the patient from whom the culture was obtained.

As with the symptoms, the pathologic changes (table 2) were not essentially different from those observed in the rabbits dying after the injection of cultures of streptococci received from Rosenow, and the description previously given would apply equally well here. Again, the only gross changes in the brain apparently consisted of a congestion of the cortical vessels. Six of the fifteen animals examined (40 per cent) had hemorrhagic edema, and four (27 per cent) showed subpleural hemorrhages. Congestion of the kidneys was observed in only seven instances, and there was nothing especially characteristic about this.

A meningeal exudate was noted grossly in only one case (cultures later showed the presence of many hemolytic staphylococci in the brain of this rabbit), but microscopic examination of sections from the brains of thirteen of the rabbits showed some degree of meningitis to be the most constant and conspicuous pathologic change in every case. A purulent meningeal exudate was especially marked in two animals, both of which had been inoculated with material containing many staphylococci. However, in other animals also (including those from which pure cultures of green colony streptococci were obtained from the brain at death and those dying at various times from sixteen to seventy hours after the inoculation), a more or less marked infiltration of the arachnoid with a mixture of large lymphocytes and polymorphonuclear cells was seen in practically every section through any region of the brain (*2 F*). In those animals that had lived longest, the lymphocytes often predominated in the exudate, although the polymorphonuclear leukocytes were also abundant. Infiltrations of the same mixture of the cells were observed in the nerve tissue subjacent to the meninges, and there were occasional small areas of necrosis, with many polymorphonuclear cells in which gram-positive cocci could be stained, but all these lesions appeared to be due to an extension of the reaction from the meninges. Perivascular cuffing was observed in sections from only about half the animals, and when present it nearly always occurred about the superficial vessels only. Rarely a vessel was seen surrounded by a cuff made up exclusively of lymphocytes, but usually many polymorphonuclears, as well as lymphocytes, were present. Aside from an occasional swollen (edematous) ganglion cell, no changes were observed in the nerve elements.

Passage Cultures.—Two pure strains of green colony streptococci, recovered from the brains of rabbits dying after inoculation with the primary cultures from the nasopharynges of patients with typical acute encephalitis were selected for further experiments. The rabbits which had been inoculated with the respective primary cultures (and from which these strains were recovered) had shown the symptoms and the pathologic changes which appeared to be most characteristic of this experimental infection of rabbits.

One strain (designated En 24) was passed through three rabbits in succession, so that the last rabbit received this strain in its fourth animal passage. Strain En 29 was put through five successive passages in rabbits but was injected each time in the same dose into several animals, giving a total of twenty-seven rabbits receiving this strain. Throughout the period during which these cultures of streptococci were under study, they were never permitted to grow in brain broth for more than twelve hours before transplantation to a new culture tube or injection into another rabbit. The animals were inoculated in all cases with 0.1 cc. of a 1:1,000 dilution of a ten to twelve hour old dextrose-brain broth culture. All the thirty rabbits inoculated with these strains died, the great majority in forty-eight hours or less.

The illness in these animals followed the course already familiar in other rabbits inoculated earlier, and the outstanding clinical features were observed in most characteristic form. The percentage incidence of the various symptoms in this group of animals is almost identical with that observed in the rabbits inoculated with the primary cultures from the patients with encephalitis or with Rosenow's cultures (table 1). Neither strain En 24 nor strain En 29 produced severe respira-

tory symptoms, but this and other clinical features varied in degree from animal to animal as they did in previously inoculated groups of rabbits. When our detailed notes and cinematographic records of symptoms were compared, there seemed to be no room for doubt that these rabbits had the same disease as that produced with the strains of green colony streptococci from patients with encephalitis selected and pronounced typical by Dr. Rosenow (fig. 1 *B, C, D* and *E*).

The virulence of the organisms cultured and the character of the symptoms produced were not materially changed as a result of passage in animals. The three rabbits inoculated in series with strain En 24 showed almost identical behavior, and the death of each occurred at almost exactly the same hour after inoculation. Similarly, there were no consistent differences in the effects produced by the strain En 29 throughout the five successive passages in animals, and certainly there was no evidence of an increase in the severity of the symptoms, although some differences were noted in the frequency of certain individual pathologic changes. If anything, the symptoms seemed to be slightly less severe in the fourth and fifth passages, though death occurred after about the same interval.

It should be noted that the individual rabbits composing the groups of from five to eight animals which were inoculated at the same time with the same dose of the passage strain En 29 did not exhibit identical behavior and that certain symptoms were much more prominent in some of the rabbits than in others of the same group. The amount of retraction, drooping and twisting of the head, the intensity of the ocular symptoms, the appearance of paralysis in the hindlegs and the degree of respiratory difficulty all varied in different rabbits inoculated with the same material. The difference in intensity of particular symptoms among such rabbits was at least as great as any similar differences between rabbits inoculated with different strains.

Both the gross and the microscopic pathologic changes in the thirty rabbits inoculated with strain En 24 or En 29 were essentially of the same character as those seen in the rabbits inoculated with Rosenow's cultures (table 2). Hemorrhagic edema in the lungs occurred in 42 per cent of the animals. In the brain a moderate degree of meningitis and some perivascular infiltration of the superficial vessels, mostly with polymorphonuclear cells, was observed in all the animals examined (fig. 2 *B*). This meningitis appeared to be somewhat intensified with successive passage in animals, so that with strain En 29, for example, clouding of the meninges and spinal fluid was observed grossly in six of eight (75 per cent) of the rabbits receiving this material in its fifth passage, whereas only one of five (20 per cent) showed a visible meningeal exudate on the second passage of this strain. A similar increase in the meningeal reaction occurring as the result of repeated successive passages in animals has been noted by Rosenow.

At the autopsy of fourteen of the rabbits inoculated with strains En 24 and En 29 cultures from the brains of the animals yielded pure growths of green colony streptococci. These organisms were also present in the heart blood from two animals of the five from which the blood was cultured.

Strain HBr-1, From the Brain of a Patient with Epidemic Encephalitis.—An apparently pure culture of green colony streptococci was obtained by us in dextrose-brain broth inoculated with ventricular fluid secured at the autopsy of a patient with encephalitis. In view of the origin of this culture (strain HBr-1) its effects in the rabbit are of special interest. The usual dose of a young (eighteen hour) growth in dextrose-brain broth of the freshly isolated organism (0.1 cc. of a 1:1,000 dilution administered intracerebrally) killed a rabbit in about twenty hours. The symptoms were first noticeable in about ten hours and were chiefly character-

ized by dyspnea of increasing severity, while trembling, ataxia and other symptoms of nervous disorder were present but less prominent.

The brain of this rabbit showed grossly only a moderate engorgement of the cerebral vessels and otherwise no change. Microscopic examination revealed a marked exudation into the arachnoid and about the vessels, consisting almost entirely of polymorphonuclear leukocytes. Some infiltration of these cells was also noted in the nerve tissue subjacent to the meninges. Otherwise no changes were noted. There was present an advanced hemorrhagic edema in the lungs. A pure growth of green colony streptococci developed in cultures made from the brain of this rabbit after death, while the culture of the heart blood was sterile.

Thus, both the symptoms and the pathologic changes in this animal followed the pattern noted in other inoculated rabbits previously described, and nothing more or less distinctive or reminiscent of human encephalitis was noted.

RESULTS OF INOCULATION OF ANIMALS WITH CULTURES OBTAINED BY US FROM NORMAL PERSONS

Primary Cultures from the Nasopharynx.—The primary cultures in dextrose-brain broth from the nasopharynges of ten normal persons (six of whom were residents not of St. Louis but of Washington, D. C.), were injected intracerebrally into albino rabbits in exactly the same manner as similar cultures from the nasopharynges of patients with encephalitis.

The dose in all cases was 0.1 cc. of a 1 : 1,000 dilution of the eighteen to twenty-four hour old culture in broth. One of the rabbits receiving a culture from a resident of St. Louis showed no symptoms whatever (possibly because of technical error in the inoculation). Two of the animals inoculated with cultures from persons in Washington, D. C., showed moderately severe respiratory and nervous symptoms, but after a few days they recovered completely, except for slight ataxia. The remaining seven rabbits—three receiving primary cultures from the nasopharynges of normal persons in St. Louis and four receiving similar primary cultures from residents of Washington, D. C.—died, making a total mortality of 70 per cent. One of these rabbits did not die for nearly five days, but all the others died in forty-eight hours or less.

The illness in these rabbits was of the same character as that seen in the animals inoculated similarly with primary cultures from the nasopharynges of patients with encephalitis. As may be seen by inspection of table 1, the percentage incidence of the principal symptoms did not vary in any significant way from that in the other groups of rabbits inoculated with material from persons with encephalitis. However, there did seem to be this difference: the symptoms in most of the animals appeared somewhat more slowly, and in the first eighteen to twenty-four hours after the inoculation they were noticeably milder. But, as already mentioned, the animals died at about the same time after inoculation (average forty hours). There was no consistent difference in the effects produced in the rabbits by inoculation with cultures from well persons in the zone of the epidemic (St. Louis) who might conceivably have been in contact with a patient with encephalitis or with a carrier and of those from healthy persons residing in Washington, D. C., where the possibility of such contact was practically nil.

It was again apparent that the green colony streptococci in the injected cultures played the principal rôle in causation of symptoms and death in the rabbits. The

particular primary cultures used for the inoculations were chosen from among other cultures from the nasopharynges of healthy persons because they appeared to contain considerable numbers of these streptococci. The blood agar plates made from each inoculum at the time of inoculation showed that green colony streptococci were present in all instances, but they were mixed with a greater variety of other organisms, including many more diphtheroid bacilli and staphylococci, than were usually present in the primary cultures from patients with encephalitis. It seems probable that this accounts in part for the somewhat slower and milder course of the infection and for the accentuation of the signs of meningeal irritation, such as the marked retraction of the head seen in several of the rabbits. At autopsy, green colony streptococci were recovered from the brains of six of the rabbits, four times in pure culture, and also from the heart blood in three instances.

Passage Cultures.—Reinjection into rabbits apparently demonstrated that some of the passage strains of these green colony streptococci originating from normal throats were somewhat less virulent than the strains similarly obtained from the nasopharynges of patients.

Of the four such passage strains injected, two killed rabbits in the usual dose in less than twenty-four hours; a third strain produced the familiar symptoms but in moderate form and the animal lingered for fourteen days before it finally died, while the fourth strain caused no illness whatever.

It must be noted that, although some of these strains from normal throats appeared to be less virulent for rabbits than streptococci from patients with encephalitis, the character of the illness produced by any of them did not differ materially from that caused by the most typical of the "encephalitis" streptococci.

Furthermore, the pathologic changes in the rabbits receiving either the unpurified primary cultures or the passage cultures from normal throats were essentially identical with those previously described (table 2). Indeed, some sections of the brain showed more marked damage to the nerve tissue (proliferation of glia cells and perivascular infiltration, with lymphocytes predominating) than was seen in sections from the brains of rabbits inoculated with cultures from patients. The most consistent and conspicuous pathologic change, as before, was a meningeal exudate, mainly of a purulent type.

IMMUNOLOGIC RELATIONSHIP OF THE STREPTOCOCCI TO CLINICAL ENCEPHALITIS

Agglutination Tests with Convalescent Serums.—Since in the preceding studies no clear or consistent differences could be made out (in either the clinical or the pathologic features) between the illness which followed the intracerebral inoculation of rabbits with streptococcus-containing material from patients with encephalitis and that which occurred when similar material from healthy persons was injected, further experiments were indicated.

With the view of discovering any specific immunologic relation of the streptococci isolated to clinical encephalitis we first made agglutination tests with convalescent serum.

In carrying out these tests a number of serums were especially chosen—four from patients from whom we had isolated streptococci possessing the characteristic virulence for rabbits, five from other convalescent patients and five from monkeys surviving an attack of the experimental virus encephalitis. All these serums had been shown by Smadel and Muckenfuss to possess distinct protective power against the virus in mice. In addition, as controls, specimens of serum from six normal persons were tested.

As test organisms we selected twelve pure strains of streptococci. Three of these were among those obtained from Dr. Rosenow; one strain was isolated from a normal throat and in preliminary tests was found to be strongly agglutinated by Rosenow's serum, and eight strains were chosen as typical of those isolated by us from patients with encephalitis. Among the latter were four strains secured from the very patients whose serums were to be tested. Also included was the strain HBr-1, which was isolated originally from the brain of a patient who died of encephalitis.

All the tests were performed at the same time, suspensions of the organisms prepared from young, actively growing brain broth cultures, diluted to the same density, being employed as antigens. The tubes were incubated for two hours at 37 C. and then placed in the icebox overnight before the final reading.

No change in the appearance of the suspensions was detectable at the end of the two hour incubation period. After the suspension had stood overnight, an irregular ring of granular sediment formed at the bottom of some tubes, although the supernatant fluid remained uniformly clouded. That this sedimentation had no significance as an index of specific agglutination was clearly shown by the fact that the same strains showed a similar sediment in the control tubes which were set up with normal serums. Thus, these tests indicated the absence of any specific agglutinating power against the streptococci on the part of any of the convalescent serums.

Protection Tests with Convalescent Serums and with Rosenow's "Encephalitis Antistreptococcus Serum."—Obviously another means of investigating the question of the part played by streptococci in the causation of epidemic encephalitis was that of testing the power of convalescent serum to protect rabbits against typical encephalitis strains. This seemed all the more worth while since the encephalitis which was transmissible to mice by the injection of the St. Louis virus could be prevented by the simultaneous injection of convalescent serum.

Consequently a series of experiments were performed to test the protective power of the convalescent serum from human patients and also from monkeys inoculated experimentally with the virus. For control inoculations normal human serum and normal horse serum and Rosenow's encephalitis antistreptococcus serum, which, according to Rosenow, should have a specific protective effect against encephalitis streptococci, were used.

The cultures employed for the intracerebral inoculation of rabbits in these experiments were the passage strains of proved virulence En 29 and Ros. 3. Mixtures consisting of equal parts of the various serums and the ten to twelve hour old dextrose-brain broth cultures, diluted 1:500, were allowed to stand at

room temperature for about two hours before injection as recommended by Rosenow. Blood agar plate cultures made as a routine at the time of injection showed that the mixtures in every instance contained a pure strain of living green colony streptococci. In a few instances the serums were injected intravenously, and an hour later the cultures in 1:1,000 dilution were injected intracerebrally.

One of the protocols, illustrating a typical experiment, is shown in table 3. The results shown in this protocol are typical of those observed in all similar experiments. The control inoculations (first three animals) showed that the culture was virulent, causing a characteristic illness, and that neither normal human serum nor normal horse serum modified in any way the course of the infection in the rabbits. Rosenow's serum, however, had a definite, though only partial, protective

TABLE 3.—*Protection Experiment* *

Animal No.	Inoculum	Symptoms	Death
1	Culture alone	Characteristic and marked in 16 hours; severe in 24 hours	30 hours
2	Culture plus normal human serum	Mild for 30 hours; then sudden development of fatal illness	36 hours
3	Culture plus normal horse serum	Characteristic, beginning within 16 hours	30 hours
4	Culture plus human encephalitis convalescent serum 499	Mild for first 20 hours; then rapidly advancing, typical illness, severe, with collapse in about 27 hours	31 hours
5	Culture plus undiluted Rosenow's encephalitis antistreptococcus serum	Edema of eyes in 16 hours; otherwise no symptoms for about 40 hours; thereafter increasing weakness and protracted collapse	3 days
6	Culture alone, 1 hour after intravenous injection of 1.5 cc. of a mixture of 0.5 cc. each of three different human encephalitis convalescent serums	Characteristic, beginning within 16 hours	29 hours
7	Culture alone, 1 hour after intravenous injection of 1.0 cc. of undiluted Rosenow's encephalitis antistreptococcus serum	Characteristic; marked within 16 hours	29 hours

* Albino rabbits weighing from 1,750 to 2,200 Gm., inoculated intracerebrally with 0.1 cc. of a fifteen hour old culture of strain En 29^2 Br R 12 A, diluted with broth 1:1,000, or with mixtures of this culture 1:500 and equal amounts of the serums listed, after the mixtures had stood at room temperature for two and one-half hours.

effect, causing considerable delay in the appearance of symptoms, while the animal eventually died. In the same circumstances the human convalescent serum had no protective effect whatever (fig. 1 *F, G, H, I, J, K* and *L*).

When injected intravenously an hour before the intracerebral introduction of the culture, neither the convalescent serum nor Rosenow's antistreptococcus serum offered the slightest detectable protection; on the contrary, the illness seemed, if anything, more acute.

Similar experiments were conducted with a total of seven different serums (five from convalescent human patients and two from convalescent monkeys). Four of the seven serums used had been tested and found to have marked protective power against the virus in mice. A summary of the results of all the protection experiments is given in table 4.

These results clearly indicate that Rosenow's serum had some protective power, though it was sufficient only to delay the death of the rabbits. This was to be expected, since this serum is a polyvalent antistreptococcus serum. On the other hand, no evidence was found that any of the convalescent serums, despite their proved power to neutralize the virus of encephalitis, could protect rabbits in any degree against the effects of intracerebral inoculation with the streptococci.

TABLE 4.—*Results of Protection Experiments*

Inoculum*	Number of Rabbits Inoculated	Symptoms	Average Time Before Death§
Culture alone	4	Characteristic, acute	32 hours
Mixtures of culture plus normal human serum	5	Characteristic, delayed in one case	30 hours (except one that lived 4½ days)
Mixtures of culture plus normal horse serum	4	Characteristic, acute	30 hours
Mixtures of culture plus human convalescent serum (5 different serums)†	7	Characteristic, acute	30 hours
Mixtures of culture plus monkey convalescent serum (2 different serums)‡	4	Characteristic, delayed in one case	24 hours (except one that lived 51 hours)
Mixtures of culture plus Rosenow's encephalitis antistreptococcus serum	5	Mild and delayed	3 days
Culture alone intracerebrally, 1 hour after intravenous injection of human convalescent serum	2	Characteristic and very acute in one case, somewhat delayed in the other	48 hours
Culture alone intracerebrally 1 hour after intravenous inoculation of Rosenow's encephalitis antistreptococcus serum	2	Characteristic, very acute	24 hours

* Intracerebral dose in all cases was equivalent to 0.1 cc. of a 1:1,000 dilution of the ten to twelve hour old dextrose-brain broth cultures.

† Two of these serums had been tested and found to have marked protective power for mice against the encephalitis virus of Muckenfuss, Armstrong and McCordock.

‡ Both these serums had strong protective power against the encephalitis virus when tested in mice.

§ Death occurred within forty-eight hours in all animals inoculated.

SUMMARY AND COMMENT

In this paper are described the results which followed intracerebral injection into animals of unpurified primary cultures from the nasopharynges and pure cultures of streptococci originating from patients with encephalitis in St. Louis and from normal persons. For comparison with the cultures secured by us we studied the pathogenicity of strains selected by Dr. Rosenow as typical examples of the encephalitis streptococcus and we also observed rabbits inoculated personally by Dr. Rosenow. Experiments designed to investigate through agglutination reactions and protection tests the capacity of encephalitis convalescent

serums to exhibit specific immunologic reactivity toward the streptococci are reported.

Of twenty-three albino rabbits inoculated intracerebrally with the primary dextrose-brain broth cultures isolated from the nasopharynges of twenty-one different patients with encephalitis, one showed transient symptoms only, followed by complete recovery, four showed no symptoms and eighteen (78 per cent) had progressive illness and died, in most instances in about forty-eight hours after the inoculation. Similar injections of the primary cultures from the nasopharynges of ten normal persons, six of whom resided at a considerable distance from the zone of the epidemic (Washington, D. C.) caused no symptoms in one rabbit, illness followed by partial recovery in two other rabbits and a rapidly fatal infection in the remaining seven rabbits, a mortality of 70 per cent.

Green colony streptococci were recovered from the brains of nearly all the animals dying after inoculation with primary cultures from the nasopharynx (whether these originated from patients with encephalitis or from normal persons), and frequently these streptococci were the only organisms isolated from the brain. On the other hand, these organisms were cultivated from the blood stream in a much smaller proportion of the rabbits.

Pure strains of streptococci recovered from the brains of the rabbits inoculated with the primary cultures from patients with encephalitis were reinjected into a total of thirty rabbits, and an intracerebral dose of 0.1 cc. of a 1 : 1,000 dilution of the young cultures was invariably fatal. There was little change in virulence observed through as many as five successive passages in animals. Strains of streptococci recovered from the brains of rabbits dying after injection of primary cultures from normal persons caused the same type of illness on reinjection into rabbits, but some of the strains were apparently somewhat less virulent than the streptococci originating from patients with encephalitis.

For comparison with the effects produced in these rabbits by injection of our own cultures, we were able to observe the reactions of a total of eighteen rabbits inoculated with streptococci isolated by Dr. Rosenow and regarded by him as representing typical encephalitis strains. Four of these animals were inoculated by Dr. Rosenow personally in our laboratory, and the remainder were inoculated by us with cultures which he sent to us. The course of the illness in these animals was practically identical with that in the rabbits inoculated with our cultures from patients with encephalitis and there seems to be no reason to doubt that we reproduced the same condition with our material as was demonstrated and described to us by Dr. Rosenow as the typical experimental encephalitis in rabbits.

In all cases the illness in the rabbits followed a fairly uniform, and to a certain degree predictable, course irrespective of the purity of the culture of streptococci injected. There was noted, however, much variation in the intensity with which particular symptoms developed in individual rabbits receiving the identical material as well as among those inoculated with cultures of different origin, and we were impressed by the ease with which a distorted impression of the whole clinical picture may be obtained if one gives special attention to changes in behavior of a particular kind or attaches special significance to a particular symptom.

Lacking the extensive experience of Dr. Rosenow which permits him to differentiate the effects produced in rabbits by injection of streptococci from patients with encephalitis from those which follow similar intracerebral injection of streptococci from patients with poliomyelitis or from other sources, we were unable to see anything definitely resembling either epidemic encephalitis or other specific human disease in the symptoms shown by these inoculated rabbits.

This conclusion is further supported by the changes noted at autopsy. The pathologic changes, like the symptoms, were of the same general character in all the rabbits examined, no matter what the source of the inoculum. The principal gross change, seen in two thirds of the seventy-two rabbits which came to autopsy, consisted in marked engorgement of the vessels of the leptomeninges. Visible meningeal exudate was present in about one third of the animals. A few more than half of the rabbits showed hemorrhagic edema of the lungs.

The sections from the brain showed on microscopic examination mainly a cellular infiltration of the meninges, with a mixture of many polymorphonuclear leukocytes and usually a smaller number of lymphocytes. The brain tissue subjacent to the meninges was often seen to be infiltrated with a similar mixture of cells. Streptococci were readily demonstrated in the meningeal exudate. Most of the sections revealed a purulent exudate in the ventricular cavities. The degree of frank meningitis apparently increased somewhat in successive passages in animals of typical encephalitis strains of streptococci. Many of the blood vessels, particularly those in the superficial cortical layers, were surrounded by cuffs consisting of polymorphonuclear cells and large lymphocytes, but only rarely could one find perivascular cuffing with round cells only. There were no significant changes in the nerve cells. No relationship could be detected between the severity of the lesions and the origin of the strain of infecting organisms. In short, the pathologic changes were mainly those of purulent meningo-encephalitis, and the lesions evidently did not correspond either in character or distribution with those characteristic of epidemic encephalitis in human patients.

Dr. Rosenow, on several occasions, in personal conversation and in published papers [6] has expressed the view that even though a filtrable virus were demonstrated in encephalitis, this would not necessarily destroy the force of his claim for the etiologic rôle of streptococci, since he conceived it to be possible that the virus and the streptococci may be biologically related and that the cocci may represent only the visible and cultivable forms of the virus. The results of our experiments with monkeys and with convalescent serums would tend to refute such a conception.

A Macacus rhesus monkey inoculated intracerebrally with a heavy dose of one of Rosenow's strains (which possessed all the characteristics regarded by him as typical of encephalitis streptococci) showed mild symptoms only for a few hours after inoculation, followed by rapid and complete recovery. This illness in the monkey was of quite different character from that produced in the same species of monkey by intracerebral inoculation with the filtrable virus recovered by Muckenfuss, Armstrong and McCordock from patients with encephalitis in St. Louis. In rabbits, the same culture of this strain, greatly diluted, produced the usual acute illness, followed soon by death. On the other hand, both Muckenfuss and Webster have shown that rabbits are entirely insusceptible to the St. Louis virus.[7]

Several specimens of the serum from patients convalescing from encephalitis failed to agglutinate any of the several strains of typical encephalitis streptococci tested and did not protect rabbits when mixed with the streptococci before intracerebral injections, while at the same time these serums did protect mice against the virus. This is further evidence that the virus and the streptococci are not related.

CONCLUSIONS

In reviewing the entire study it seems clear that most of the observations of Rosenow were confirmed, but the principal inferences he has drawn from them do not appear to be valid.

Specifically, we found, in agreement with the published findings of Rosenow, (1) that green colony streptococci tend to be relatively more abundant in the nasopharynges of patients acutely ill with encephalitis than in those of normal persons, (2) that the streptococci originating from the nasopharynges of patients with encephalitis often exhibit a somewhat greater degree of virulence for rabbits when tested by intra-

6. Rosenow, E. C.: Weekly Bull. St. Louis M. Soc. **28**:69 (Oct. 13) 1933; Relation of Streptococci to Filtrable Virus of Epizootic Encephalitis of Fox, J. Infect. Dis. **48**:304 (March) 1931.

7. Report on the St. Louis Outbreak of Encephalitis, Public Health Bulletin no. 214, Washington, D. C., Superintendent of Documents, Government Printing Office, 1935, p. 30.

cerebral inoculation than those similarly cultured from normal persons, (3) that these streptococci also possess apparently a slightly greater serologic homogeneity when tested by agglutination with Rosenow's "encephalitis antistreptococcus serum" and (4) that the medium (dextrose-brain broth) and technical procedures of Rosenow are especially well adapted to the isolation and study of the streptococci.

On the other hand, we did not confirm Rosenow's findings that a certain narrow range of cataphoretic velocity is characteristic of "encephalitis streptococci." In our hands no consistent relationship between the source or virulence of the cultures of streptococci and their average velocity in the electric field was evident. Moreover, while it was true that either mixed primary cultures or pure cultures of green colony streptococci from patients with encephalitis produced in rabbits an acute illness of more or less constant character, this experimental infection could not be regarded as identical with human epidemic encephalitis, on the basis either of the symptoms or of the pathologic changes. No suggestion of a biologic relationship between the streptococci and the virus isolated from patients in St. Louis was indicated by our results. Lastly, we found no evidence that encephalitis convalescent serum had any specific reactivity toward the streptococci isolated from patients with encephalitis.

In view of the occasional isolation by Rosenow, as well as by other investigators, of green colony streptococci from specimens of the brain or spinal fluid of patients with encephalitis and the relative abundance of streptococci of this type, having a high virulence for rabbits, in the nasopharynges of patients during the height of the disease, it does not seem justifiable to dismiss these organisms altogether from consideration. We conclude, however, that no valid evidence has been adduced which would support the view that the streptococci represent the primary etiologic agent of epidemic encephalitis in human beings or have any specific relationship to the virus isolated from patients with this disease in St. Louis. It appears that by insisting on identifying the streptococci as the primary etiologic agent Rosenow has missed the opportunity to elucidate their possible rôle as secondary invaders.

PURPURA HAEMORRHAGICA FOLLOWING THE ADMINISTRATION OF NEOARSPHENAMINE

THE REACTION TO NEOARSPHENAMINE COMPARED WITH THE REACTION TO MAPHARSEN

ERNEST H. FALCONER, M.D.
AND
NORMAN N. EPSTEIN, M.D.
SAN FRANCISCO
AND
GEORGE K. WEVER, M.D.
STOCKTON, CALIF.

Hemorrhage following the therapeutic use of the arsphenamines apparently was not reported until 1916, when Evans [1] mentioned the occurrence but did not connect it definitely with arsphenamine. Three years later (1919) two French observers, Labbé and Langlois,[2] called attention to the fact that purpuric manifestations are a complication of the arsphenamine therapy of syphilis. McCarthy and Wilson [3] in 1932 reviewed the published reports of eleven cases of purpura haemorrhagica following the use of arsphenamine and reported two of their own cases. Loveman [4] in 1932 was able to find reports of fourteen instances of purpura haemorrhagica following arsphenamine treatment up to 1931, when his article was sent to the publishers. With one new case included in his report, the total number of cases reported up to 1932, on the basis of Loveman's statistics, was seventeen (including the two cases reported by McCarthy and Wilson). Since 1932 there have been nearly as many instances reported of purpura haemorrhagica following the intravenous use of arsphenamine as during the previous

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From the Division of Medicine and the Division of Dermatology, of the University of California Medical School.

1. Evans, F. A.: Observations on the Origin and Status of the So-Called "Transitional" White Blood Cell, Arch. Int. Med. **17**:1 (Jan.) 1916.

2. Labbé, M., and Langlois, S.: Purpura hémorrhagique aigue par intoxication arsénicale, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:786, 1919.

3. McCarthy, F. P., and Wilson, Robert, Jr.: The Blood Dyscrasias Following the Arsphenamines, J. A. M. A. **99**:1557 (Nov. 5) 1932.

4. Loveman, A. B.: Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines, Ann. Int. Med. **5**:1238 (April) 1932.

eighteen years.[5] This does not mean that the condition is relatively more frequent but probably indicates a more widespread interest and alertness in the recognition of complications due to arsphenamine, so that more instances are now being reported.

It is not our purpose to attempt a comprehensive review of the literature. The articles by Loveman [4] and McCarthy and Wilson [3] contain comprehensive bibliographies. In a review of the recent literature on blood Sturgis and his associates [6] mentioned the available reported instances of purpura haemorrhagica following arsphenamine therapy occurring from 1932 to 1935.

In the syphilis clinic at the University of California since 1924 about sixty thousand treatments with arsphenamine have been administered, with four recorded cases of purpura haemorrhagica. The data on three of the patients, the first observed in 1931 and the other two from 1932 to 1935, constitute the material for this report.

METHODS AND TECHNIC

Three patients were studied. One was observed in the University of California Hospital during the acute phase of the condition, and was later followed in the clinic; but he soon disappeared from observation, and his subsequent history is unknown. Two patients were followed in the hematologic clinic as ambulatory patients.

Blood counts were made with standardized pipets; the hemoglobin was estimated by means of the Sahli method as modified by Osgood and Haskins.[7] With this method 13.7 Gm. of hemoglobin per hundred cubic centimeters of blood equals 100 per cent. The Rees and Ecker [8] method of estimating the number of platelets was used, with from 300,000 to 400,000 platelets per cubic millimeter of blood considered as the normal range. Blood counts were made between 9:00 and 10:30 a. m., usually before but at times just after treatment was given, and

5. Rich, Murray: An Unusual Hematologic Reaction to Neoarsphenamine, J. A. M. A. **101**:1223 (Oct. 14) 1933. Bickford, J. V., and Tilghman, R. C.: Purpura Haemorrhagica in Congenital Syphilis Following Arsphenamine, ibid. **100**:1984 (June 24) 1933. Kostoulas, A.: Hémorragies des muqueuses post-"néo 606" et sulfarsénobenzolique, Bull. Soc. franç. de dermat. et syph. **40**:771, 1933. Chevallier, P.; Colin, M.; Bernard, J., and Ely, Z.: Sur les formules sanguines des syndromes hémorragiques toxiques: A propos de six cas d'hémorrhagies post-arsénobenzoliques recueillis en un an, Sang **6**:917, 1932. Grund, J. L.: Purpura Hemorrhagica with Profuse Bleeding from the Mucous Membranes Following the Treatment of Syphilis with Bismarsen, New England J. Med. **211**:443 (Sept. 6) 1934. Niles, H. D.: Hemorrhagic Purpura Following Bismarsen (Arsphenamin-Bismuth Preparation), Am. J. Syph. & Neurol. **18**:300 (July) 1934.

6. Sturgis, Cyrus C.; Isaacs, Raphael; Goldhamer, S. M.; Bethell, F. H., and Farrar, G. E.: Blood: A Review of the Recent Literature, Arch. Int. Med. **55**: 1001 (June) 1935.

7. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107, 1923.

8. Rees, H. M., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, J. A. M. A. **80**:621 (March 3) 1923.

were carried out in the building in which the syphilis clinic is located. The sedimentation tests and the hematocrit readings were made with Wintrobe pipets.[9]

The capillary resistance tests were made with the da Silva-Mello capillary resistometer as modified by Dalldorf.[10] This instrument is a suction syringe attached by a rubber tube to a small glass cup, with a cuff, 8 mm. in width, turned out at right angles. The syringe has attached to it a spring manometer for registering the number of centimeters of mercury of negative pressure in the cup. We applied the cup to the skin of the outer surface of the upper portion of the arm, just above the elbow; the number of petechiae produced at the end of one minute, with various levels of negative pressure, constituted the readings. After consulting with Dr. James Rinehart, of the department of pathology, who lent us the resistometer and who has made many readings in his study of subclinical scurvy, we decided to adopt the following standard: A reading of 20 cm. or less, producing from six to twenty or more petechiae, indicates a decrease in the capillary resistance.

REPORT OF CASES

CASE 1.—J. O'C., a white man aged 34, single, consulted a physician in 1931 on account of a urethral discharge, headache and general malaise. The Wassermann reaction of the blood was positive, and the patient was treated for syphilis. He received twenty-four injections each of neoarsphenamine and of a bismuth preparation. He recalled that on two occasions (dates not remembered) bleeding of the gums occurred after an injection of neoarsphenamine and that later some "purplish spots" appeared over the lower extremities. He did not mention this to his physician at the time.

No antisyphilitic treatment was administered from November 1931 to December 1932 (thirteen months). At the end of this period the patient reported to the urologic clinic of the University of California on account of a urethral discharge. As the Wassermann reaction of the blood was four plus, he was transferred to the syphilis clinic for treatment, where the diagnosis of latent syphilis was made and therapy was instituted.

The patient received twelve weekly injections of a preparation of bismuth in oil intramuscularly. On April 18, 1933, he received an intravenous injection of 0.45 Gm. of neoarsphenamine. During the next two weeks he received two injections of 0.6 Gm. each. One week later, on May 9, he received the fourth injection, 0.6 Gm. of neoarsphenamine. Immediately after this injection the patient had a severe headache, became nauseated and vomited. One hour after the injection his gums began to bleed, and three hours later many "small purplish spots" began to appear below the knees, gradually spreading upward to the trunk and arms. Eleven hours after the injection he voided dark and smoky-appearing urine. The gums continued to bleed during the night, and in the morning a black, tarry stool was passed. The patient returned to the syphilis clinic within twenty-four hours after the injection and was transferred at once to the medical service of the University of California Hospital.

Examination showed that the skin and mucous membranes were pale and that numerous petechial hemorrhages were scattered over the body, especially on the extremities. The pupils were of unequal sizes, the right being larger than the left,

9. Wintrobe, M. M.: Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles, Proc. Soc. Exper. Biol. & Med. **27**:1071, 1930.

10. Dalldorf, Gilbert: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933.

and both reacted sluggishly to light. The heart and lungs appeared normal. The blood pressure was 100 systolic, and 60 diastolic. The right epididymis was enlarged and tender. The urine showed a trace of albumin; many red blood cells were present in the sediment.

The bleeding time (Duke's method) was found to be six hours. The clotting time (Lee and White) was eight minutes, and the clot did not retract after six hours. The application of a tourniquet above the elbow caused the appearance of many more petechiae below the tourniquet. The blood counts are shown in table 1.

Immediately after entry into the hospital the patient was given 15 cc. of his own blood intramuscularly and then 20 units of parathyroid extract and an erythema dose of ultraviolet radiation to the back and chest. The bleeding continued. Twelve hours after admission to the hospital the patient was given a transfusion of 240 cc. of whole blood from a compatible donor. Within a half-hour the bleeding stopped and did not recur.

On the following morning the bleeding time was five minutes. The patient felt perfectly well and insisted on leaving the hospital.

TABLE 1.—*Data on the Blood Counts in Case 1*

Date, 1933	Hemoglobin		Red Blood Cells, Millions	Reticulocytes, %	White Blood Cells, Thousands	Polymorphonuclears, Percentage			Eosinophils, %	Lymphocytes, %	Monocytes, %	Platelets, Thousands
	%	Gm.				Total	Filament	Nonfilament				
5/11	..	....	....	0.6	11.75	63	38	25	5	18	13	30
5/13	72	9.9	3.87	...	11.65	75	60	15	2	12	11	80
5/15	..	....	....	...	.....	76	59	17	5	15	4	280
5/17	..	....	....	...	.....	..	..	..	..	..	..	410
6/ 7	..	....	....	0.6	.....	69	57	12	8	16	7	430
6/12	80	11.0	4.97	...	10.90	78	64	14	3	12	9	320
6/27	..	....	....	...	.....	61	56	6	5	22	10	340

CASE 2.—G. N., a white woman aged 48, married, had been under treatment for syphilis for about three months. The date of the initial infection was not known. The treatments were begun on June 24, 1933. She had had no previous treatment for syphilis, although the diagnosis was made fifteen years previously, when the Wassermann reaction of the blood was positive.

After twelve intramuscular injections of a suspension of bismuth in oil, she received an intravenous injection of 0.3 Gm. of neoarsphenamine. She had chilly sensations, headache and nausea for twenty-four hours after the injection. On October 12, one week later, she was given a second intravenous injection of neoarsphenamine, of 0.15 Gm. Within a few minutes she became nauseated, and later in the evening generalized pains developed over the body, more particularly through the lumbar region and down the lower extremities. A few hours after the onset of pain "black and blue" spots appeared over the lower extremities. This was approximately eight hours after the administration of neoarsphenamine. The patient did not report to the syphilis clinic until October 19. At that time the skin and subcutaneous tissue below the knees showed dark ecchymotic areas, which were not elevated but were slightly tender. They varied in size from patches 1 to 2 mm. in diameter to areas about 3 by 5 cm. in extent. The bleeding time (Duke) was three minutes, and the clotting time (Lee and White) was ten minutes. The clot was firm and retractile. The ecchymotic areas and purpuric eruption had disappeared by October 25.

On November 13 the bleeding time (Duke) was three minutes, and the clotting time (Lee and White) was ten minutes with a 10 mm. test tube. Between Nov. 15, 1933, and May 21, 1934, she received twenty-four intramuscular injections of 0.2 Gm. each of bismuth subsalicylate. Intramuscular injections of mercury salicylate were attempted but were abandoned in favor of the bismuth subsalicylate on account of pain. She also took 1 cc. of potassium iodide three times daily by mouth.

On May 29, owing to changes in the clinic staff, she was inadvertently given 0.3 Gm. of neoarsphenamine. After the injection she had nausea, vomiting, chills and general malaise, and on the following morning there were a few purpuric spots on the buccal mucous membrane. On June 4 she received another dose of 0.3 Gm. of neoarsphenamine, followed by an exactly similar general reaction. On the following morning (about twenty-four hours later) the skin of the extremities and trunk was covered with a purpuric eruption, with scattered areas of large ecchymotic patches, the largest about 8 by 10 cm. There were areas of ecchymosis in the buccal mucosa and over the pharynx from 2 mm. to 1 cm. in diameter.

The platelet count on June 6 was 10,000. The bleeding time was sixteen minutes; the clotting time, six minutes. The clot was nonretractile. Table 2 shows the results of the studies of the blood that were made.

Examination on June 6, aside from the marked purpura and ecchymosis mentioned and a palpable edge of the liver, did not show any objective signs resulting from the blood dyscrasia. The spleen was not palpable. No actual bleeding had occurred. The patient's dietary was carefully gone into at this time, but it showed no deficiency. There was no history of exposure to drugs or chemicals that might affect the hematopoietic system. It will be noted that the platelets were rapidly regenerated and that the red and white blood cells were only slighly disturbed. The bleeding time had returned to normal by June 9. Studies on capillary resistance by means of the Dalldorf apparatus [10] showed a lag in the return of capillary resistance to normal, according to the standard used. It will be noted that the increase of capillary resistance was slower than the rate of the platelets in returning to normal. By July 12 there were a few minute petechiae (two or three) at a pressure of 20 cm. of mercury.

On October 18 we sent for this patient in order to try out carefully the effects of one of the new arsenical preparations, mapharsen.[11] It will be seen from table 2 that the blood was normal at this time. The first dose, 10 mg., did not produce any reaction. The table shows the immediate and the twenty-four hour variations in the platelet count. She received one injection of 10 mg., two injections of 20 mg. and two injections of 30 mg., making a total of five injections, after which injections were discontinued because the hemoglobin value and the white blood cell count showed a slight fall. She had no untoward reactions from any of the injections of mapharsen and expressed the opinion that she must be improving as she felt so much better. She was then given mercury salicylate, 0.1 Gm. intramuscularly each week, up to the time the blood counts were made on Jan. 10, 1935.

11. Mapharsen (the hemialcoholate of meta-amino-para-hydroxphenylarsine oxide) was supplied to us for clinical trial by Parke, Davis & Co. This preparation is obtained by the oxidation of arsphenamine and is similar to arsenoxide. It has the formula:

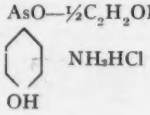

TABLE 2.—*Data on the Blood in Case 2*

Date	Hemoglobin %	Hemoglobin Gm.	Red Blood Cells, Millions	Platelets, Thousands	White Blood Cells, Thousands	Polymorphonuclears, Percentage Total	Filament	Nonfilament	Eosinophils, %	Lymphocytes, %	Monocytes, %	Notes
10/19/33	82	11.3	4.65	290	5.40							Cleared
10/25/33	82	11.3	4.92	290	5.60	73	19	54	4	15	6	
11/13/33	..	....	....	320	6.20	77	16	61	2	24	7	Bleeding time, 3 minutes; clotting time, 10 minutes
6/ 6/34	85	11.6	4.41	10	5.15	67	34	33	3	16	13	Bleeding time, 16 minutes; clotting time, 6 minutes; no retraction
6/ 7/34	..	....	....	40								Hematocrit measurements: Low / Normal / High Red cell volume, 36 cc.: 45 / 45.0 / 46 Corpuscular volume, 81.6 cu. microns: 80 / 87.0 / 94 Mean corpuscular hemoglobin, 26.3 micromg.: 27 / 29.5 / 32 Mean corpuscular hemoglobin concentration, 32.1%: 33 / 35.0 / 38 Volume index: 0.904 / 1 / 1.05 Saturation index, 0.947: 0.87 / 1 / 1.23 Sedimentation rate: 20 minutes, 5 mm.; 40 minutes, 10 mm.; normal, 2 to 4 mm. in 4 hours; fragility, hemolysis began at 0.4%, complete at 0.23%
6/ 8/34	..	....	....	50	....	..	..	..	..	..	..	Purpura fading; ecchymosis apparent
6/ 9/34	80	11.0	4.20	100	8.65	..	..	..	..	..	..	Bleeding time, 3 minutes; clotting time, 10 minutes; some retraction
6/11/34	80	11.0	4.05	160	8.55	79	47	32	2	13	5	
6/13/34	84	11.5	4.67	130	6.10							
6/15/34	77	10.4	4.08	150								
6/16/34	..	....	....	180								
6/19/34	..	....	....	181								
6/21/34	85	11.6	....	230	7.00							
6/27/34	82	11.3	4.04	300	7.60	73	17	56	2	19	6	
6/29/34	..	....	....	...	....	..	..	..	..	..	..	Sedimentation rate: 15 minutes, 2 mm.; 30 minutes, 4.5 mm.; 60 minutes, 10 mm.
7/10/34	75	11.6	3.62	200	7.00	75	18	57	2	15	8	
7/20/34	73	10.0	3.90	300	7.20	81	48	33	3	11	5	
7/27/34	83	11.2	3.84	270	4.65	61	43	18	4	24	11	
10/18/34	90	12.3	4.00	280	6.25	72	58	14	1	22	5	Before mapharsen: bleeding time, 2 minutes; clotting time 9 minutes;
				230								15 minutes after mapharsen
				220								30 minutes after mapharsen
				200								60 minutes after mapharsen
												Sedimentation rate: 15 minutes, 2 mm.; 30 minutes, 7 mm.; 60 minutes, 15 mm.
												Hematocrit measurements (before mapharsen): red cell volume, 35 cc.; corpuscular volume, 87.5 cu. microns; mean corpuscular hemoglobin, 30.7 micromg.; mean corpuscular hemoglobin concentration, 35.1%; volume index, 0.8; saturation index, 1.12
10/19/34	..	....	....	150								
10/22/34	80	11.0	4.02	230	6.65	65	40	25	1	20	13	After three treatments with mapharsen
11/ 1/34	80	11.0	3.50	370	6.10	73	50	24	..	12	4	
11/ 5/34	..	....	....	350								
11/ 8/34	90	12.3	4.48	200	7.10	80	63	17	4	10	6	
11/13/34	77	10.5	4.80	250	4.70	76	37	39	5	9	8	
11/15/34	86	11.8	4.87	290	8.80	68	46	22	1	22	8	
11/20/34	75	10.2	3.56	380	4.40	70	45	25	3	17	10	One nucleated red cell seen in counting 100 leukocytes
11/22/34	80	11.0	4.67	270	7.75	74	46	28	3	15	6	
11/28/34	85	11.7	....	250	8.20	75	40	35	2	15	8	
12/ 6/34	90	12.3	4.33	240	6.90	76	50	26	1	16	7	
12/13/34	85	11.7	4.20	250	5.75	71	42	29	5	17	7	
12/20/34	94	12.3	4.86	260	8.65							
1/10/35	86	11.8	5.31	240	5.00	79	53	26	4	13	4	

Capillary resistance	Pressure, Cm. of Mercury	Petechiae
6/14/34	15	10 to 12
6/16/34	16	6 to 7
6/27/34	12	3 to 5

The question then arose as to whether she had become in any measure desensitized to neoarsphenamine by the administration of mapharsen. The reactions to mapharsen did not suggest this, as she did not show diminishing reactions with each dose of mapharsen but showed no toxic reactions at all toward the drug. We sent for the patient again on Feb. 8, 1935, to test her sensitivity to a further small dose of neoarsphenamine. The blood count, including the platelet count, appears in table 3. As soon as the 0.1 Gm. of neoarsphenamine was administered she became ill, with nausea, chills and generalized pains associated with great prostration. Within one hour after the injection the platelet count dropped to 10,000 and purpuric spots began to appear on the buccal mucosa and about the ankles. There was slight bleeding from the gums. While vomiting over a stationary wash-bowl, she became dizzy and fell forward, striking the right orbital region against the wall. The trauma was slight, yet a large area of ecchymosis appeared immediately. The accompanying photograph (fig. 1), taken on the day following the injection,

Fig. 1 (case 2).—The purpuric and ecchymotic lesions which appeared within two hours after 0.1 Gm. of neoarsphenamine was administered.

shows the lesions on the arms which appeared two hours after 0.1 Gm. of neoarsphenamine had been given. Recovery was rapid, as will be noted in table 3.

Case 3.—J. P., an Italian ex-soldier, single, aged 37, reported in November 1931 to the medical clinic of the University of California Medical School, complaining of soreness of the tongue of two weeks' duration. He had a primary penile chancre in 1927. At that time he was given three courses of intramuscular injections of a bismuth preparation and mercury. He may have received a few intravenous injections of neoarsphenamine, but he was uncertain concerning this possibility. Examination disclosed a small, shallow ulcer about 4 mm. in diameter at the tip of the tongue. Aside from a rather slow pulse rate (66), a blood pressure of 100 systolic, and 70 diastolic and the lingual lesion, physical examination revealed no abnormality. The Wassermann reaction of the blood was positive. A diagnosis of recurrent secondary syphilis with mucous patches was made, and antisyphilitic therapy was administered, consisting first of twelve intramuscular injections of bismuth subsalicylate and two intravenous injections of 0.45 Gm. of

TABLE 3.—*Further Data on the Blood in Case 2*

Date	Hemoglobin %	Hemoglobin Gm.	Red Blood Cells, Millions	Platelets, Thousands	White Blood Cells, Thousands	Polymorphonuclears, Percentage Total	Filament	Nonfilament	Eosinophils, %	Lymphocytes, %	Monocytes, %	Comment
2/ 8/35	86	11.7	4.83	500	6.20							
2/28/35	86	11.7	4.91	300	5.20	75	50	25	11	4	10	Before neoarsphenamine was given
				60	....	..	..	..	..	..	..	15 minutes after neoarsphenamine
				50	....	..	..	..	..	..	..	30 minutes after neoarsphenamine
				40	....	..	..	..	..	..	..	45 minutes after neoarsphenamine
				20	....	..	..	..	..	..	..	1 hour after neoarsphenamine
3/ 1/35	75	10.2	4.56	20	8.55	93	21	72	3	1	3	At the end of 1 hour petechiae appeared over forehead and in mouth; gums bled; bleeding time, 4 minutes; clotting time, 6 minutes
3/ 2/35	75	10.2	....	10	8.80	86	51	35	..	6	8	Petechiae over upper and lower extremities and face
3/ 4/35	80	11.0	4.45	40	8.00	75	44	31	4	12	9	
3/ 5/35	..	....	....	40								
3/ 6/35	84	11.5	4.82	100	12.30	86	64	20	2	13		
3/ 8/35	80	11.0	4.54	230	7.80	85	70	15	2	10	3	
3/16/35	..	....	....	300								
3/21/35	85	11.6	4.52	300	7.75	77	65	8	2	8	13	
3/28/35	80	11.0	4.65	320	7.80	84	55	29	1	9	4	Bleeding time, 2½ minutes
4/ 4/35	90	12.3	5.27	250	11.70	82	50	32	5	15	3	
4/11/35	84	11.5	5.40	200	7.15	88	65	23	..	10	2	
4/18/35	90	12.3	5.06	220	5.70	74	51	23	1	14	11	
5/ 7/35	87	11.9	5.57	250	7.45	64	49	15	1	21	14	Before mapharsen
				220	....	..	..	..	..	..	..	15 minutes after mapharsen
				230	....	..	..	..	..	..	..	30 minutes after mapharsen
				200	....	..	..	..	..	..	..	1 hour after mapharsen
5/28/35	84	11.5	4.61	150	6.55	57	44	13	3	29	11	
6/10/35	90	12.3	4.77	200	11.75	69	29	40	3	11	17	
6/18/35	90	12.3	4.57	170	7.00	71	47	24	1	19	9	
6/25/35	86	11.7	4.70	180	5.85	76	50	26	3	16	5	

neoarsphenamine at intervals of seven days. Nausea followed each injection. The patient then went to another city to work, stopping treatment.

In March 1934, after two years, he returned and was referred to the syphilis clinic for a continuation of treatment. A course of eight weekly injections of 0.2 Gm. of bismuth subsalicylate intramuscularly was administered. At weekly intervals thereafter he had three intravenous injections of 0.45 Gm. of neoarsphenamine. After each of the first two injections he had chilly sensations and felt feverish, faint and nauseated. After the second injection he went to bed as soon as he reached home but felt well the following morning. Immediately after the third injection, on May 29, he felt "as if he was choking," became faint and had pain in the epigastrium. He remained lying on the table in the clinic for about a half hour and then went home to bed. He was chilly and nauseated but did not vomit. In about three hours "dark spots" appeared over the lower extremities and bleeding began at the margins of the gums. He did not notice whether the urine was dark or the stool tarry. On May 31, on examination in the hematologic clinic, the skin below the knees was thickly peppered with small purpuric spots. Over both arms were scattered ecchymotic areas and some smaller purpuric spots. There was one large ecchymotic area on the upper portion of the right arm, 8 cm. in extent, and a few purpuric spots were present in the buccal mucous membrane and over the hard palate. The spleen and liver were not palpable.

During the interval between May 31 and July 10, 1934, this patient received no antisyphilitic therapy or any other therapy but was followed in the hematologic clinic for study of the behavior of the blood following the episode of purpura. Physical examination showed him to be in fairly robust health. He was a particularly well developed, muscular man with no obvious infection other than syphilis. Careful inquiry was made into his dietary history, especially since 1915. From this period up to 1920, he was in the Italian army, part of the time in Serbia. His dietary was apparently adequate. There was no familial hemorrhagic tendency, and he did not know of any exposure to benzene or other poisons.

On July 10 he was again started on treatment. Between this date and October 6 he received twelve intramuscular injections of 0.2 Gm. of bismuth subsalicylate. At 9:00 a. m. on October 13 0.3 Gm. of neoarsphenamine was administered intravenously. Nausea, general malaise and chilly sensations followed immediately. The patient went home and to bed. In about two hours the margins of the gums about the teeth began to bleed, and purpuric spots appeared in the buccal mucosa. Within three hours large ecchymotic areas appeared on the inner aspects of both arms. On October 14 he felt chilly and weak and had generalized body pains but was up and about. The next morning he reported to the hematologic clinic. Examination showed a dense shower of purpuric spots on both lower extremities. On the inner aspects of the arms were large ecchymoses, one area measuring 7 by 5 cm. (fig. 2).

Following this episode he received no treatment of any kind until November 20, when he was given 10 mg. of mapharsen intravenously. No toxic symptoms of any type developed. He received eight doses of mapharsen, ranging from 10 to 40 mg. each. The erythrocyte, hemoglobin and platelet levels underwent no significant change while he was receiving mapharsen. He stated that he felt better than for several weeks.

On March 5, 1935, he was sent for, and with his permission 0.15 Gm. of neoarsphenamine was administered intravenously. As our second patient had remained so exceedingly sensitive to neoarsphenamine, it became necessary to know whether this patient was still as sensitive as before the course of mapharsen. From our

knowledge of the persistent nature of neoarsphenamine sensitivity, we felt that he would still be sensitive; and that proved to be the case. Immediately after the injection he became moderately prostrated; he had chilly sensations and pain in the back and lower extremities; his face was flushed, and headache and nausea were present. Within one hour after the injection the platelet count dropped to 80,000. The capillary resistometer (Dalldorf) readings showed that the capillary resistance was beginning to decrease within the same period. Within two hours after the injection purpuric spots appeared over the tibial regions, and an eccyhmotic area about 0.5 cm. in diameter appeared on the buccal mucosa. As will be noted from table 5, there was a slow return of the platelet level to normal. On the following day the patient felt recovered from his reaction except for a feeling of general malaise. He returned to work the next day, and on the fourth day after the onset of purpura several new areas appeared over the upper portion

Fig. 2 (case 3).—The purpuric and ecchymotic lesions which appeared within two hours after 0.1 Gm. of neoarsphenamine was administered.

of the arms, apparently as the result of the strain of pushing a lawn mower for part of the day.

ANALYSIS OF DATA CONTAINED IN THE TABLES

Complete studies of the blood have been made in cases 2 and 3, but no attempt will be made at this time to analyze the data other than those pertaining to the platelets and the capillary resistance. The effects of neoarsphenamine and mapharsen on the formed elements of the blood are being studied in two groups of patients under treatment for syphilis. These results together with part of the data obtained in cases 2 and 3 will be discussed in a future publication.

Table 1 (case 1) shows the rapid regeneration of platelets following the toxic reaction, with bleeding and purpura haemorrhagica. This patient had an acute toxic episode with considerable oozing of blood from the mucous membrane; yet within six days after the last injection of neoarsphenamine the platelet count had returned nearly to normal.

Date	Hemoglobin %	Hemoglobin Gm.	Red Blood Cells, Millions	Platelets, Thousands	White Blood Cells, Thousands	Polymorphonuclears, Percentage Total	Filament	Nonfilament	Eosinophils, %	Lymphocytes, %	Monocytes, %	Notes
5/31/34	85	11.6	5.01	60	8.35							
6/ 1/34	..	....	....	90								
6/ 2/34	..	....	....	100								
6/ 4/34	..	....	....	120								
6/ 5/34	..	....	....	180	....	..	..	..	..	..	..	Hematocrit measurements — Normal / Low / High Corpuscular volume, 84 cu. microns — 87 / 80 / 94 Red cell volume, 42 cc. — 45 / 45 / 46 Mean corpuscular hemoglobin, 23.4 microng. — 35 / 33 / 38 Volume index, 0.93 — 1 / 0.95 / 1.05 Mean corpuscular hemoglobin concentration, 25.4% — 35 / 33 / 38 Saturation index, 0.85 — / 0.87 / 1.23
6/ 6/34	86	11.7	5.00	150	7.60	68	41	26	..	14	19	Fragility starts at 0.40; complete at 0.35
6/ 7/34	..	....	....	160								
6/ 8/34	..	....	....	195								
6/ 9/34	..	....	4.44	220	5.45	..	..	..	..	..	..	Bleeding time 2½ minutes
6/11/34	90	12.3	5.01	250	9.60	68	47	21	..	20	10	Bleeding time, 2½ minutes; clotting time, 7½ minutes
6/13/34	92	12.6	4.66	230	5.95							Capillary Resistance — Pressure, Cm. of Mercury — Petechiae 6/14/34 — 10 — 16 6/16/34 — 10 — 4 15 — 25-30 6/22/34 — 10 — 2-4 15 — 15-20 20 — 21-25 6/26/34 — 10 — 1 15 — 4-6 20 — 6-10 7/17/34 — 15 — 0 20 — 2-4 25 — 6-8
6/15/34	..	....	....	180								
6/16/34	92	12.6	4.59	210								
6/19/34	85	11.6	4.78	270								
6/20/34	..	....	....	230								
6/21/34	..	....	5.07	280	4.05	62	56	6	2	27	9	
6/22/34	..	....	....	220								
6/26/34	83	11.3	5.15	220	8.30							
7/ 3/34	95	12.9	5.22	320	11.45	69	46	23	3	15	13	
7/10/34	95	12.9	4.44	300	7.55	68	46	22	1	21	10	
7/17/34	96	13.1	4.97	390	12.70	61	35	26	1	26	11	Many platelets on smear; 1 myelocyte
7/24/34	80	11.0	3.55	300	9.05							
7/30/34	90	12.3	4.28	270	7.40	12	53	19	3	13	12	
8/ 7/34	84	11.5	5.22	250	7.95							
8/14/34	84	11.5	4.69	210	7.90	59	38	21	5	29	12	
9/29/34	92	12.6	4.42	240	6.60	61	37	24	1	27	10	
10/15/34	90	12.3	4.60	80	8.30	76	41	35	4	8	12	
10/16/34	..	....	....	90	....	73	52	21	1	18	8	
10/18/34	..	....	....	120								
				250	11.00	..	..	..	..	..	..	Immediately after 0.5 cc. of activin intramuscularly
				230	9.80	..	..	..	..	..	..	One hour later
10/19/34	..	....	....	190	6.85							
10/20/34	90	12.3	4.84	200	12.25							
10/22/34	92	12.6	4.33	290	8.65	67	44	23	1	20	12	
10/27/34	86	11.7	4.33	250	13.20	69	37	32	6	9	15	
10/30/34	83	11.3	4.46	500	14.70	62	36	26	2	27	8	
11/10/34	86	11.7	3.93	300	13.05	82	39	43	1	12	4	Much stippling
11/19/34	85	11.6	4.07	300	13.55	88	77	11	..	8	3	
11/20/34	..	....	....	280	....	66	41	25	2	16	15	One hour after first injection of mapharsen
11/26/34	95	12.9	4.90	320	11.70	63	45	18	2	29	6	
12/ 3/34	93	12.6	5.00	230	9.35	74	47	27	1	13	11	
12/10/34	95	12.9	4.20	180	9.00	61	37	24	3	24	11	
12/15/34	95	12.9	4.33	230	6.90	66	36	30	3	26	5	
12/22/34	85	11.6	4.48	230	7.10							
12/29/34	85	11.6	4.58	340	7.60	79	69	10	1	10	5	
1/ 5/35	95	12.9	5.19	300	10.40	75	67	8	..	14	11	
1/12/35	95	12.9	....	230	9.85	64	42	22	1	24	10	
2/23/35	..	....	....	...	....	..	..	..	..	..	..	Hematocrit measurements: Red cell volume, 47 cc.; corpuscular volume, 86.5 cu. microns; mean corpuscular hemoglobin, 23.2 microng.; mean corpuscular hemoglobin concentration, 26.8%; volume index, 0.954; saturation index, 0.892; fragility started at 0.45%, complete at 0.35%

TABLE 5.—*Further Data on the Blood in Case 3*

Date	Hemoglobin %	Hemoglobin Gm.	Red Blood Cells, Millions	Platelets, Thousands	White Blood Cells, Thousands	Polymorphonuclears, Percentage Total	Polymorphonuclears, Percentage Filament	Polymorphonuclears, Percentage Nonfilament	Eosinophils, %	Lymphocytes, %	Monocytes, %	Comment
2/25/35	103	14.1	6.04	230	8.60							
3/ 5/35	95	13.0	4.93	280	11.40	66	44	22	2	21	11	Before neoarsphenamine
				140	....	..	..	..	..	..	..	15 minutes after neoarsphenamine
				80	....	..	..	..	..	..	..	1 hour after neoarsphenamine; purpuric spots began to appear in mouth about 1 hour after injection of neoarsphenamine
												Bleeding time, 3½ minutes; clotting time, 8½ minutes; normal clot retraction
3/ 6/35	..	....	....	40	8.65	70	37	33	2	13	15	
3/ 7/35	..	....	....	40	7.60	65	35	30	3	18	14	
3/ 9/35	96	13.1	5.33	40	8.70	69	36	33	3	20	8	Before mapharsen
												15 minutes after mapharsen
3/11/35	..	....	....	80	8.60	71	45	26	..	24	5	
3/15/35	100	13.7	....	130	6.80	57	44	13	..	33	9	
3/18/35	96	13.1	5.51	200	6.30	65	45	20	2	22	11	
3/20/35	92	12.5	4.89	200	8.60	53	35	18	3	43	13	
3/24/35	100	13.7	....	240	6.75	68	45	23	4	14	14	
3/30/35	90	12.3	5.03	280	8.00	63	44	19	2	23	12	
4/15/35	84	11.5	4.12	240	6.40	63	42	21				
5/17/35	84	11.5	4.71	220	6.65	60	42	18				
5/24/35	90	12.3	5.50	160	6.85	..	..	..	..	..	..	Before mapharsen
				160	....	..	..	..	..	..	..	15 minutes after mapharsen
				140	....	..	..	..	..	..	..	1 hour after mapharsen
5/31/35	86	11.7	5.03	170	7.10	67	31	16	1	19	13	Before mapharsen
				160	....	..	..	..	..	..	..	15 minutes after mapharsen
				180	....	..	..	..	..	..	..	30 minutes after mapharsen
				180	....	..	..	..	..	..	..	1 hour after mapharsen
6/ 1/35	86	11.7	4.67	200	6.50	68	47	21	..	22	10	24 hours after mapharsen
6/14/35	86	11.7	4.38	250	7.65	53	29	24	6	28	13	

Table 2 (case 2) shows that after the first toxic episode, on Oct. 12, 1933, the platelets were so rapidly regenerated that one week later (October 19), when the patient reported to the hematologic clinic, the platelet count had returned to normal. Two days after the second purpuric episode, which occurred on June 6, 1934, the platelet count was 10,000 per cubic millimeter. It required twenty-one days for the platelet level to return to normal. On Feb. 28, 1935, the day on which she received 0.1 Gm. of neoarsphenamine for the experimental production of purpura (table 3), the platelet count before the injection was given was 300,000 per cubic millimeter. Fifteen minutes after the injection was given the count had fallen to 60,000; within one hour to 20,000, and at the end of forty-eight hours, to 10,000. At the end of seventeen days the platelet level was again 300,000 per cubic millimeter. The results of the capillary resistance tests (Dalldorf resistometer) made on the outer aspect of the upper portion of the left arm were as follows:

Date	Pressure, Cm. of Mercury	Petechiae
3/ 1/35	20	25+
	15	15+
	10	3+
3/ 6/35	20	12+
	15	10+
	10	1+
3/28/35	20	10+
	15	10+
	10	1+
4/11/35	25	3 to 6 (normal)
	20	1+ (normal)

There appears to have been a definite lag in the return of the capillary resistance as compared to the rate of return of the platelet count to normal.

After the first administration of mapharsen (10 mg.) a fall of 130,000 platelets per cubic millimeter of blood occurred after twenty-four hours. The same type of immediate effect on the platelet level is noted after the initial dose of 30 mg. of mapharsen at the beginning of the second course of treatments on May 7. The platelets dropped during this second course of mapharsen to levels well below what we consider normal.

Table 4 (case 3) shows that two days after the toxic reaction and the appearance of purpura haemorrhagica the platelet count was 60,000 per cubic millimeter of blood. The patient had received three doses of 0.45 Gm. of neoarsphenamine before the advent of frank purpuric manifestations. The return of the platelet count to normal was slow, requiring thirty-three days. Table 4 also shows that the capillary resistance (Dalldorf resistometer) lagged behind the return of the platelets to normal. The effect of a peptone preparation on the platelet level is shown after the second attack of toxic purpura haemorrhagica. Following the injection of this preparation intramuscularly the platelet count rose from 120,000 to 250,000 in one hour, but twenty-four hours later it had dropped to 190,000, suggesting that the initial rise was a redistribution phenomenon. The return of the platelet count to normal after the second toxic episode was more rapid, requiring only fifteen days. The injection of the peptone preparation might have been a factor in bringing about this shorter period, as compared with the first period of thirty-three days.

Table 5 (case 3) shows that after the injection of 0.15 Gm. of neoarsphenamine, on March 5, 1935, for the experimental production of purpura, the platelet count fell to 40,000 at the end of twenty-four hours and gradually rose until March 30, when it had reached 280,000. During the second course of treatment with

mapharsen the count again fell below normal levels. The estimations of capillary resistance (Dalldorf resistometer) in the upper portion of the left arm were as follows:

Date	Pressure, Cm. of Mercury	Petechiae
3/5/35	25	10+
	20	20+
	15	10+

These readings were taken one hour after 0.15 Gm. of neoarsphenamine had been injected. It was obvious that the resistance was decreasing while the tests were in progress.

Date	Pressure, Cm. of Mercury	Petechiae
3/7/35	20	18+
	15	10+
3/9/35	25	15+
	20	10+
	15	7+

It was about fifteen days before the readings were within the normal range. In this instance the return of the capillary tone was more rapid than the return of the platelets, which showed a marked lag.

SENSITIVITY TO ARSENIC

The suggestion naturally presents itself in connection with the absence of a toxic reaction after the administration of mapharsen that the quantity of arsenic is the important factor. Mapharsen contains less arsenic according to atomic weight than neoarsphenamine. About 19 per cent of neoarsphenamine is arsenic, while mapharsen contains 29 per cent. One tenth gram of neoarsphenamine, which was the amount used in our last sensitivity tests, contains about 19 mg. of arsenic. Forty milligrams of mapharsen, which was the largest dose administered to our two patients, contains 12 mg. of arsenic. It does not seem probable that the quantitative difference between 19 and 12 mg. of arsenic would account for a sharp toxic reaction with one dose and no reaction with the other. However, the reaction to arsenic, as exhibited by various patients, must have a quantitative factor. The question arises as to whether there is not some product formed by the oxidation of arsphenamine in the body that is responsible for the toxic reactions. In order to investigate this question further, we tested the second and third patients to different combinations of arsenic, complete blood counts being made before and after each test.

Arsenic	Case 2	Case 3
Solution of potassium arsenite, 1 cc. daily for 1 week	No change in blood count; no change in platelet level	No change in blood count; no change in platelet level
2 cc. of sodium cacodylate, 19% strength	Before intravenous injections, 160,000 platelets; one-half hour after injections, 160,000 platelets; no change in blood count	Before injection, 210,000 platelets; one-half hour after injection, 220,000 platelets; no change in blood count
Tryparsamide, 2 Gm. intravenously	Before injection, 180,000 platelets; 15 minutes after injection, 200,000 platelets; 1 hour after injection, 170,000 platelets; no noteworthy change in blood count	Before injection, 200,000 platelets; 15 minutes after injection, 230,000 platelets; 1 hour after injection, 220,000 platelets; monocytes rose from 13% before to 25% 1 hour after injection

Some persons are so sensitive to solution of potassium arsenite that 1 or 2 drops well diluted in water will cause nausea and gastro-intestinal irritation. In our cases 2 and 3 no untoward effects were noted. Intravenous injections of both sodium cacodylate and tryparsamide likewise did not cause untoward symptoms, and no hemorrhagic or purpuric manifestations occurred. The platelet counts of both patients were below normal when these tests were carried out (between July 6 and Aug. 6, 1935), but it should be recalled that three episodes of toxic purpura following the injection of neoarsphenamine and two courses each of mapharsen preceded these tests.

From the data obtained, we believe that these two patients were not sensitive to inorganic arsenic and that they were not sensitive to arsenic in combination with benzene, as evidenced by the absence of reaction to 2 Gm. of tryparsamide. They were obviously sensitive to the combination of arsenic in the neoarsphenamine radicle.

COMMENT

These three patients showed two distinct types of sensitivity to neoarsphenamine. The first patient became increasingly sensitive until a crisis occurred in the form of a severe reaction followed by purpura haemorrhagica. He was sensitive in 1931 during the first course of neoarsphenamine treatment, for he recalled at least two occasions when he had mild hemorrhagic manifestations. Apparently no nitritoid reaction preceded the bleeding. The fact that he received no arsenicals and no treatment of any kind for a year did not suffice to abolish the sensitivity, as evidenced by the severe reaction after the fourth dose of neoarsphenamine in the second series of treatments. This patient's response to neoarsphenamine stresses the importance of a careful inquiry concerning previous reactions before arsphenamine or its derivatives is administered.

The other two patients belong to a group, probably small, that present an initial sensitivity to neoarsphenamine. The second patient presented marked hypersensitivity to the drug from the standpoint of a toxic reaction of the platelets and capillaries. McCarthy and Wilson [8] in their reports collected from the literature cited one case in the thrombocytopenic group in which the complication occurred a few days after the fifth dose of neoarsphenamine. This case was reported by Jensen.[12] Such cases illustrate that sensitivity is not dependent on the amount of the drug previously administered. Our second patient had not received any arsphenamine previous to Sept. 28, 1933, when she received her

12. Jensen, Julius: Purpura Hemorrhagica Following Neoarsphenamin, Minnesota Med. **12**:689 (Nov.) 1929.

first dose of neoarsphenamine. After the second dose of 0.15 Gm. purpuric manifestations appeared. She had a nitritoid reaction after each dose. It is important to recall that when she reported to the hematologic clinic one week after receiving the second dose, although the purpuric spots were still well marked, the platelets had returned to a normal number and the bleeding time was normal. Were it not for subsequent observations, we probably would have considered the hemorrhagic manifestations as purpura simplex. The marked sensitivity to neoarsphenamine presents a sharp contrast to the entire lack of any untoward reaction from mapharsen. This applies to both the second and the third patient and certainly suggests that the sensitivity is not to arsenic as such but to some oxidation product not present in mapharsen. This is of considerable importance, as Cole and his co-workers [13] after a study of one thousand, two hundred and twelve patients treated with arsphenamine or its derivatives stated:

> In a number of instances the patient was sensitive to more than one type of arsphenamine so that, even after a premonitory symptom caused a change in the type of arsphenamine used, the patient experienced a second and in some instances a third reaction, or even more; in fact, there were 338 actual complications found among the 214 persons. . . . if the patient is susceptible to one arsenical, the chances of using another are lessened, and this sensitivity persists.

This refers to all complications and reactions and not specifically to purpura haemorrhagica, but the latter is a complication of such severe toxicity that one would naturally hesitate to use any further arsphenamine. The question as to whether mapharsen can be safely used after the occurrence of purpura haemorrhagica is answered in the affirmative by the results in our two cases but requires further observation.

SUMMARY AND CONCLUSIONS

Three cases are reported in which severe toxic constitutional reactions accompanied with purpura haemorrhagica followed the administration of neoarsphenamine. One of the patients showed sensitivity after several injections of neoarsphenamine; the other two presented an initial sensitivity to the drug.

Evidence is offered suggesting that the actual amount of arsenic entering the circulation is not the important factor in determining the toxic reaction, although it may be one factor; the important factor is probably some oxidation product formed by the breaking down of neoarsphenamine in the body.

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13. Cole, H. N.; DeWolf, Henry; McCuskey, J. M.; Miskjian, H. G.; Williamson, G. S.; Rauschkolb, J. R.; Ruch, R. O., and Clark, Taliaferro: Toxic Effects Following Use of the Arsphenamines, J. A. M. A. **97**:897 (Sept. 26) 1931.

No toxic reaction, no purpura haemorrhagica and no significant fall of the platelet count occurred after the administration of mapharsen.

Our studies suggest a distinct relationship between nitritoid crises following the administration of arsphenamine and its derivatives and the development of thrombocytopenic purpura haemorrhagica. This relationship stresses the importance of making blood counts for all patients who show nitritoid reactions after the administration of the arsphenamines.

We have demonstrated the fact that the capillary lesion is as important as the thrombopenia as a factor in the production of the purpuric manifestations.

INFECTIOUS MONONUCLEOSIS

FURTHER STUDIES

C. A. STUART, PH.D.

HENRY WELCH, PH.D.

JOHN CUNNINGHAM, M.D.

AND

ALEX M. BURGESS, M.D.

PROVIDENCE, R. I.

The interest in infectious mononucleosis stimulated by the work of Paul and Bunnell [1] continues to increase, as is shown by the number of publications on the subject that have appeared since these investigators established a serologic test for diagnosing the condition.

In a previous report [2] the clinical and cytologic aspects of the disease were reviewed. Serologic analyses of the serums of thirteen patients were given, and the nature of the sheep cell antibodies in the blood of these patients was discussed. A modification of the test originally devised by Paul and Bunnell was introduced as an aid in the diagnosis of borderline cases. This modification has eliminated or confirmed suspicious clinical observations in many cases but has failed to do so in others. The serologic diagnosis of infectious mononucleosis in the early stages of the disease or when there is mild involvement is frequently hampered by the presence of normal sheep heterophile antibodies in the blood of the patient. Our principal purpose in the present communication is to show that it is now possible to detect the presence of sheep heterophile antibodies due to infectious mononucleosis even in serum containing normal heterophile antibodies in excess. Using the technic to be described, a diagnosis of the disease can be made before the original test of Paul and Bunnell or our modification shows definitely positive results. Serum sickness in which there is also an increase in the sheep heterophile antibodies [3] can be distinguished from infectious

From the Department of Biology, Brown University, and the Bureau of Public Health and the Bureau of Communicable Diseases, Hartford, Conn.

1. Paul, J. R., and Bunnell, W. W.: Am. J. M. Sc. **183**:90, 1932.

2. Stuart, C. A.; Burgess, A. M.; Lawson, H. A., and Wellman, H. E.: Some Cytologic and Serologic Aspects of Infectious Mononucleosis, Arch. Int. Med. **54**: 199 (Aug.) 1934.

3. (*a*) Davidsohn, I.: J. Immunol. **18**:31, 1930. (*b*) Stuart, C. A.; Tallman, Juanita, and Brintzenhoff, Esther: ibid. **28**:85, 1935.

mononucleosis, and, furthermore, a correct diagnosis can be made when a patient is suffering from both diseases.

In table 1 are shown the titers of the serums of twenty patients with infectious mononucleosis who have not previously been reported on. For the most part, from two to five tests were made for each patient at intervals during the course of the disease. In each case, however, only the highest titer is recorded in the table. Agglutinating titers for sheep cells in the different cases ranged from 1:160 to 1:10,240, and lytic titers ranged from 1:320 to 1:10,240.

TABLE 1.—*Titers for Sheep Cell Antibodies in the Serum of Persons with Infectious Mononucleosis* *

	Agglutinins													Lysins											
Case Number	5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240	20,480	5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240	20,480
29	4	4	4	4	4	4	4	4	4	4	3	2	1	0	4	4	4	4	4	4	4	4	4	4	3	1	0
30	4	4	4	4	4	4	4	4	4	3	1	0	0	0	4	4	4	4	4	4	4	4	4	4	3	1	0
31	4	4	4	4	4	4	4	4	4	4	3	1	0	0	4	4	4	4	4	4	4	4	4	3	2	0	0
32	4	4	4	4	3	1	0	0	0	0	0	0	0	0	4	4	4	4	4	3	1	0	0	0	0	0	0
33	4	4	4	4	4	4	4	4	4	3	1	0	0	0	4	4	4	4	4	4	4	4	4	3	2	0	0	0
34	4	4	4	4	4	4	4	4	3	2	0	0	0	0	4	4	4	4	4	4	4	4	3	1	0	0	0	0
35	4	4	4	4	4	4	4	2	0	0	0	0	0	0	4	4	4	4	4	4	4	4	2	0	0	0	0	0
36	4	4	4	4	4	4	4	4	4	4	3	2	0	0	4	4	4	4	4	4	4	4	4	4	3	1	0	0
37	4	4	4	4	4	4	4	4	4	3	2	0	0	0	4	4	4	4	4	4	4	4	4	4	3	1	0	0
38	4	4	4	4	3	2	1	0	0	0	0	0	0	0	4	4	4	4	4	4	4	3	1	0	0	0	0	0
39	4	4	4	4	4	4	4	4	4	2	1	0	0	0	4	4	4	4	4	4	4	4	4	4	2	0	0	0
40	4	4	4	4	4	4	4	3	2	1	0	0	0	0	4	4	4	4	4	4	4	4	3	1	0	0	0	0
41	4	4	4	4	4	4	4	4	4	2	1	0	0	0	4	4	4	4	4	4	4	4	4	3	2	1	0	0
42	4	4	4	4	4	4	4	3	2	1	0	0	0	0	4	4	4	4	4	4	4	4	3	1	0	0	0	0
43	4	4	4	4	4	4	4	4	3	1	0	0	0	0	4	4	4	4	4	4	4	4	4	2	1	0	0	0
44	4	4	4	4	4	4	3	2	0	0	0	0	0	0	4	4	4	4	4	4	3	1	0	0	0	0	0	0
45	4	4	4	4	4	4	4	4	4	3	1	0	0	0	4	4	4	4	4	4	4	4	4	3	2	0	0	0
23-46	4	4	4	4	4	3	1	0	0	0	0	0	0	0	4	4	4	4	4	4	4	2	0	0	0	0	0	0
29-47	4	4	4	4	4	4	4	3	2	0	0	0	0	0	4	4	4	4	4	4	4	3	2	0	0	0	0	0
48	4	4	4	4	4	3	1	0	0	0	0	0	0	0	4	4	4	3	2	0	0	0	0	0	0	0	0	0

* 4 signifies a complete reaction; 3, 2 and 1 signify a partial reaction, and 0, signifies no reaction.

It will be noted that in every case the titers of the two antibodies are practically parallel. This is somewhat unusual, as pointed out by Meyer,[4] since the injection of heterophile antigen into appropriate laboratory animals produces high lytic titers with little or no agglutinating antibodies for sheep cells. Ash,[5] working in these laboratories, obtained lytic titers of 1:80,000 for sheep cells, while the agglutinating titer of the same serums was only 1:40 or 1:80 after the prolonged immunization of rabbits with heterophile antigens. This seems to indicate either

4. Meyer, K.: Med. Klin. **29**:981, 1933.

5. Ash, R.: Personal communication to the authors.

that the antigen concerned in the production of sheep cell antibodies in infectious mononucleosis is different from those commonly encountered or that the reaction of man to heterophile antigens in general is different from that of most animals. This seems not impossible, as the injection of horse serum which contains heterophile antigen into man frequently produces a marked increase both in sheep cell agglutinins and in lysins, the increases in the titers of the two antibodies often being parallel. As Bailey and Raffel [6] pointed out, one ordinarily anticipates a much higher lytic than agglutinating titer for heterologous erythrocytes in normal or immune blood of man or of animals, yet we have found that the agglutinins for rabbit cells in normal human serum greatly exceed the lysins for these cells. It will be shown in a subsequent paper that the injection of type A human cells into a rabbit may on occasion produce a high agglutinating titer for these cells without materially increasing the lytic titer. Such considerations, while lacking practical application at the present time, are of great theoretical interest, as they relate to the controversial unitarian hypothesis of antibodies.

In the course of infectious mononucleosis there is usually a sharp rise in the number of heterophile antibodies in the blood, followed in several days by a gradual lowering of the titer. In a few cases the titer completely disappeared about two weeks after the first appearance of the antibodies. Case 29, on the other hand, represents the opposite extreme. The first specimen of blood taken during the acute stage of the disease showed an agglutinating titer of 1:10,240, and this titer persisted for over one month. At the end of approximately two and one-half months the last specimen taken still gave a titer of 1:320. Fifteen of our patients were tested from six months to one year after recovery from the disease, but in no case were antibodies of the infectious mononucleosis type present.

It should be pointed out here that in our investigation both agglutinins and lysins were studied. For diagnostic purposes, however, it is more satisfactory to work with agglutinins in this disease, because variation from the average normal titer appears to be far less with this type of antibody.

In order to obtain more information regarding the nature of the sheep cell agglutinins in infectious mononucleosis, serums giving a positive reaction were adsorbed with raw and boiled cells and with emulsions of kidney (beef, rabbit, guinea-pig, swine, cat and chicken). In these experiments 0.5 cc. of the cells or 0.15 cc. of the tissue emulsion was added to 2 cc. of a 1:2.5 or a 1:5 dilution of the serum. The tubes were then kept at room temperature for one hour. After centrifugation the supernatant fluid was removed, a portion was tested for sheep cell

6. Bailey, G. Howard, and Raffel, Sidney.: J. Clin. Investigation **14**:228, 1935.

agglutinins and the remainder was readsorbed. This procedure was repeated until three adsorptions with the various antigens were completed.

These adsorption tests showed that of all the cells and tissues used only beef cells removed the increased agglutinins from the serum of patients with infectious mononucleosis. It has already been shown [7] that the failure of sheep cells to agglutinate in such serums after successive adsorption with highly turbid emulsions of guinea-pig kidney, as reported in a previous paper,[2] was not due to the specific adsorption of the heterophile antibodies.

The fact that beef cells, either raw or boiled, remove the sheep heterophile agglutinins from the serum of persons with infectious mononucleosis is important, since it will be shown later in this paper that these cells do not remove the sheep heterophile agglutinins from normal serum. If after the adsorption of a serum with beef cells the titer for

TABLE 2.—*Adsorption of Selected Normal Serum and Serums of Persons with Infectious Mononucleosis and with Serum Sickness*

	Normal Serum*									Serum of Persons with Infectious Mononucleosis									Serum of Persons with Serum Sickness								
Serum Adsorbed with Beef Cells and Guinea-Pig Kidney	5	10	20	40	80	160	320	640		5	10	20	40	80	160	320	640		5	10	20	40	80	160	320	640	
Before adsorption.....	4	4	4	4	4	4	2	0		4	4	4	4	4	3	1	0		4	4	4	4	4	3	1	0	
After adsorption with beef cells.....	4	4	4	4	4	4	2	0		0	0	0	0	0	0	0	0		2	0	0	0	0	0	0	0	
After adsorption with guinea-pig kidney.....	0	0	0	0	0	0	0	0		4	4	4	4	4	3	1	0		0	0	0	0	0	0	0	0	

* This serum was tested both before and after adsorption with a 0.05 per cent suspension of sheep cells rather than with the usual 0.5 per cent suspension, which accounts for the exceptionally high normal titer.

sheep cells is completely or materially reduced, the serum is not normal. Bailey and Raffel [6] have reported similar findings. Unfortunately, a final diagnosis of infectious mononucleosis after adsorption with beef cells only is open to two objections: In the early stages of the disease, if the normal heterophile agglutinins are in excess of those due to infectious mononucleosis it will be impossible to make a correct diagnosis. Furthermore, if horse serum has been injected into the patient, there will usually be a marked increase in the sheep heterophile agglutinins, which will also be adsorbed by beef cells.

Table 2 shows the results of the adsorption with beef cells and guinea-pig kidney of a selected normal serum with a high titer and of the serum of a person with infectious mononucleosis and of the serum of a person with serum sickness adjusted to the same sheep cell titer as the normal serum. It will be noted that the sheep cell antibody from

7. Stuart, C. A.: Proc. Soc. Exper. Biol. & Med. **32**:861, 1935.

normal serum is not removed by beef cells but is completely removed by guinea-pig kidney. On the other hand, the reverse is true of the serum of a person with infectious mononucleosis; beef cells adsorb the antibody, and guinea-pig kidney does not. The increased sheep cell antibody in the serum of a person with serum sickness is adsorbed by both beef cells and guinea-pig kidney. Therefore, the adsorption of a serum with both the cell and the tissue specified eliminates all possibility of confusing the serum of a person with infectious mononucleosis with either a normal serum of high titer or the serum of a person with serum sickness.

It seems from this that the sheep heterophile agglutinins in the three types of serum are all different. This aspect of the question, together with the relation of these antibodies to the heterophile antigen in human cells of types A and AB, has been discussed in a previous paper.[7a]

Since it can easily be ascertained whether in an apparent case of infectious mononucleosis horse serum has recently been injected, it might appear that a test differentiating between these two diseases is superfluous. Davidsohn,[8] however, reported an increase in the sheep cell antibodies in the blood of patients from one to three years after treatment with horse serum. The following cases further emphasize the necessity of such a test:

REPORT OF CASES

CASE 23-46.—The patient was admitted to the Charles V. Chapin Hospital on Feb. 17, 1935, with a condition suggestive of meningitis. Therapeutic serum was administered, and later the meningococcus was isolated from both the nasopharyngeal secretion and the spinal fluid. Serum sickness developed, and the serum was tested and adsorbed according to our routine procedure. Table 3 (February 27) clearly shows that the sheep cell antibodies were of the type present in serum sickness. Two weeks later more serum was obtained. In experiments not connected with this investigation the serum reacted peculiarly. It was then adsorbed with beef cells and guinea-pig kidney, with the results shown in table 3 (March 14). The complete removal of the sheep cell agglutinins by beef cells and the failure of guinea-pig kidney to adsorb this antibody completely after three successive adsorptions made it apparent that antibodies of the type found in infectious mononucleosis as well as those of the type found in serum sickness were present in the serum.

CASE 29-47.—D. A., a 7 year old boy, was admitted to the hospital on April 14, 1935, with signs and symptoms suggestive of meningitis. The spinal fluid showed intracellular gram-negative diplococci, which were later grown in culture. The diagnosis was meningococcic meningitis.

Lumbar puncture was performed every day from April 14 to 20, inclusive. Serum obtained from the Massachusetts Board of Health was administered as follows: 1 vial intraspinally, 2 vials intracisternally, 2 vials intramuscularly and

7a. Stuart, C. A.; Fulton, MacDonald; Ash, Roy P., and Gregory, K. K.: J. Infect. Dis. **59**:65, 1936.

8. Davidsohn, I.: J. Immunol. **16**:259, 1929.

2 vials intravenously on April 14; 3 vials intraspinally on April 15, and 1 vial by each route on April 16 to 19, inclusive.

The temperature was irregular but elevated until April 20, when it reached 99 F. The maximum temperature was 105 F. on April 15. The curve of the pulse rate corresponded with that of the temperature. The temperature remained at 99 F. or lower until April 25, when it rose and was irregularly maintained until May 2. Urticaria was noted, and a diagnosis of serum sickness was made. The maximum rise in temperature in this episode was to 103 F. On May 3 the temperature rose to 103.8 F., and it remained irregularly elevated until May 8, when it reached 106.4 F. by rectum. On May 3 enlargement of the cervical lymph nodes was noted both anteriorly and posteriorly. The axillary nodes, especially in the left axilla, and the inguinal nodes were enlarged. At this time "real tonsillitis" with exudate was noted and treated by irrigations with solution of sodium

TABLE 3.—*Absorption of Serums from Patients in Cases 23-46 and 29-47*

Case	Date		5	10	20	40	80	160	320	640	1,280	2,560	5,120	10,240
23-46	2/27/35	Before adsorption	4	4	4	4	4	4	4	3	2	0	0	0
		After adsorption with beef cells	2	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea-pig kidney	0	0	0	0	0	0	0	0	0	0	0	0
	3/14/35	Before adsorption	4	4	4	4	4	4	4	4	4	3	1	0
		After adsorption with beef cells	2	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea-pig kidney												
		First adsorption	4	4	4	4	3	1	0	0	0	0	0	0
		Second adsorption	4	4	4	4	2	0	0	0	0	0	0	0
		Third adsorption	4	4	4	4	2	0	0	0	0	0	0	0
29-47	4/21/35	Before adsorption	4	4	4	4	4	4	3	1	0	0	0	0
		After adsorption with beef cells	0	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea-pig kidney	0	0	0	0	0	0	0	0	0	0	0	0
	5/9/35	Before adsorption	4	4	4	4	4	4	4	4	3	2	0	0
		After adsorption with beef cells	0	0	0	0	0	0	0	0	0	0	0	0
		After adsorption with guinea-pig kidney												
		First adsorption	4	4	4	4	4	3	2	0	0	0	0	0
		Second adsorption	4	4	4	4	4	3	1	0	0	0	0	0
		Third adsorption	4	4	4	4	4	3	1	0	0	0	0	0

chloride. A diagnosis of infectious mononucleosis was suggested, and the record stated that enlargement of the glands had persisted longer than is usual in serum sickness.

On May 8 the temperature was 106.4 F. by rectum; the pulse rate, 164, and the respiratory rate, 40. The patient was pale and alert and did not appear to be in a toxic condition. The ears were normal. The throat was slightly infected, and the tonsils were enlarged. The neck was not stiff. The glands were not so greatly enlarged but were noticeable in the neck, axillae, epitrochlear region and groins. Percussion revealed that the heart was slightly enlarged. There was a moderately loud, blowing systolic murmur.

On May 8 blood culture showed growth of a weakly hemolytic streptococcus.

Microscopic examination of the blood on May 8 revealed 20,000 leukocytes, 78 per cent polymorphonuclears, 14 per cent small lymphocytes, 1 per cent large lymphocytes, 7 per cent endotheliocytes (or monocytes) and 1 per cent eosinophils.

Comment.—In this case, as in case 23-46, the diagnosis was meningococcic meningitis. Horse serum was injected and serum sickness developed. The serum was tested and adsorbed in the usual manner. The sheep cell agglutinins, according to the tests reported here and to others, were clearly typical of serum sickness. During the convalescence of this patient, symptoms comparable to those present in infectious mononucleosis were evident. The serum was adsorbed with beef cells and guinea-pig kidney. Table 3 shows that a result identical with that in case 23-46 was obtained. Antibodies of the type found in serum sickness were present; nevertheless, antibodies of the type found in infectious mononucleosis could be demonstrated.

CASE 43.—A third case (table 1) involving meningococcic meningitis but different from the two cases just discussed is of interest. A few hours after the patient's admission to the hospital meningococci were observed in the spinal fluid. A test of the serum was positive for infectious mononucleosis. The patient died twenty-four hours later. The strain of Meningococcus isolated from the spinal fluid failed to adsorb any sheep heterophile antibodies from the serum.

It is possible, of course, that the connection between meningococcic meningitis and infectious mononucleosis in the cases reviewed was merely coincidental. Five other patients with meningococcic meningitis showed no symptoms of infectious mononucleosis, nor could sheep cell antibodies typical of infectious mononucleosis be demonstrated at any time during the course of the disease. Bunnell [9] observed no increase in sheep cell agglutinins in several cases of the disease. Yet until more is known about the etiology of infectious mononucleosis, such observations should not be overlooked. The importance of these observations lies not so much in the causal relation of the meningococcus to infectious mononucleosis as in the association of the organism in infections of the upper respiratory tract to infectious mononucleosis. There is some question in the minds of many physicians who have encountered infectious mononucleosis as to whether it is a disease entity or merely an unusual reaction to an infection of the upper respiratory tract caused by any of a number of organisms.

The uncertainty as to the status of the disease as an entity is heightened by the fact that cases occur in which the clinical picture is doubtful. A mild infection of the upper respiratory tract or an infection of the throat, associated with slight tenderness and moderate or marked enlargement of the cervical lymph nodes and a blood picture in which the percentage of lymphocytes is higher than usual and in which the characteristic so-called abnormal immature lymphocytes are seen in moderate number, presents a picture which may well be considered typical of a borderline condition. In cases of such a condition

9. Bunnell, W. W.: Am. J. M. Sc. **186**:346, 1933.

the serologic test has been a definite means of differentiation. In our experience, in these cases of the borderline type serologic tests for the characteristic agglutinins have almost invariably proved negative. This, coupled with the fact that the typical form of the disease is definite clinically and cytologically and a high titer for agglutinins of the type described is usually shown, has given us the impression that we are dealing with a definite entity.

However, the demonstration of agglutinins of the type found in infectious mononucleosis in the blood of patients with meningococcic meningitis, as described in this paper, is of unusual interest as a possible illustration of the occurrence of these antibodies in patients who do not show the clinical picture of infectious mononucleosis. In one of these cases (case 43) the patient died within twenty-four hours of his admission to the hospital, and no cytologic studies were made ; so the presence of coincidental infectious mononucleosis must be considered as possible. In case23-46 the serum of the patient was sent to us as a matter of routine, and cytologic studies were made. This patient, however, did not at any time present the clinical or cytologic picture of infectious mononucleosis. The case of the other patient (case 29-47), however, is of special interest in that definite clinical and cytologic data are available. A 7 year old boy, after definite serum sickness, had what the records stated was "real tonsillitis" and enlargement of the lymph nodes suggestive of infectious mononucleosis. Five days later, at a time when the cytologic manifestations of this disease would ordinarily have been at their height, the blood count showed, on the contrary, a total of 20,000 leukocytes per cubic millimeter and the following differential count (May 8, 1935) : 78 per cent polymorphonuclears, 14 per cent small lymphocytes, 1 per cent large lymphocytes, 7 per cent endotheliocytes . . . and 1 per cent eosinophils. The picture was further complicated by the fact that on the day that this specimen of blood was taken the patient showed a rise in temperature to 106.4 F. and weakly hemolytic streptococci were observed in the blood culture. Here, then, is an instance of the appearance in a patient suffering from serum sickness following treatment for meningococcic infection of a clinical picture resembling infectious mononucleosis and the coincident appearance of the agglutinins typical of the disease, without the characteristic cytologic changes.

A number of widely different bacteria have been proposed as the cause of infectious mononucleosis. Members of the streptococcus group,[1] diphtheroid bacilli [10] and Vincent's organisms [11] are terms perhaps most

10. Murray, E. G. D.; Webb, R. A., and Swann, M. B. R.: J. Path. & Bact. **29**:407, 1926.

11. Nyfeldt, A.: Compt. rend. Soc. de biol. **101**:590, 1929.

frequently associated with this disease. The close association of Vincent's angina and infectious mononucleosis has led some authors to state the belief that this association is not a mere coincidence (Gorham, Smith and Hunt [12]). The uniform failure of the organisms associated with this disease to produce heterophile antibodies in the rabbit does not rule out such organisms as the causative factor, since the heterophile antibodies in this disease are not at all comparable to those produced in rabbits by ordinary heterophile antigens.

In one of our cases (case 41) one of us (Welch) isolated a diphtheroid organism which grew sparsely on several different types of enriched medium. When freshly isolated, this organism agglutinated strongly in the serum of this patient and in the serums of four other patients known to have infectious mononucleosis. Furthermore, the organism removed small but significant amounts of sheep cell antibodies from these serums. After several transplants had been made, however, the organism completely lost its agglutinating and adsorptive properties. Heterophile antibodies were not demonstrated in rabbits into which this organism had been injected, nor did large doses of the living organism affect rabbits adversely. Through the courtesy of Caspar G. Burn it was possible to compare this organism with two strains of Listerella monocytogenes (Murray and his associates [10]) and with two strains similar to Murray's organism isolated by Burn [13] from the blood of patients with meningo-encephalitis. No significant morphologic, biochemical or serologic relationship has as yet been demonstrated between the four strains obtained from Burn and the organism isolated in our case 41.

COMMENT

The value of the serologic test devised by Paul and Bunnell in the diagnosis of infectious mononucleosis has been clearly demonstrated in several recent papers. The test as ordinarily applied, however, is not wholly specific, since normal serum of high titer may occasionally be reported as giving a positive reaction. Furthermore, persons into whom horse serum has been injected frequently show high titers for sheep cell agglutinins which by routine agglutination tests cannot be distinguished from those of patients with infectious mononucleosis. The adsorption of the serum of a patient suspected of having infectious mononucleosis with both beef cells and emulsions of guinea-pig kidney permits a complete analysis of the type or types of sheep heterophile antibodies present. Only the complete removal of these antibodies by guinea-pig kidney indicates a normal serum; the adsorption of all or most of the antibodies by beef cells and their complete adsorption by guinea-pig

12. Gorham, L. W.; Smith, D. T., and Hunt, H. D.: J. Clin. Investigation **7**:504, 1929.

13. Burn, C. G.: Proc. Soc. Exper. Biol. & Med. **31**:1095, 1934.

kidney indicates a serum of the type present in serum sickness. In the majority of cases a diagnosis of infectious mononucleosis can be made clinically and serologically without the aid of adsorption tests, but their use in doubtful cases in which there is a low titer or in which complications of serum sickness are present makes possible a sure diagnosis.

These findings clarify the diagnosis of infectious mononucleosis but contribute little to the question of the actual origin of the antibodies under consideration. It is conceivable that the antibodies are of intrinsic origin, that they are, in a sense, auto-antibodies produced in response to the release into the blood plasma of a protein normally confined to the body cells. If this were true it would not be so difficult to explain the presence of the increases in sheep cell antibodies in diseases other than infectious mononucleosis such as have been reported in this paper and by Paul and Bunnell,[1] Ramsdell and Davidsohn,[14] Bernstein,[15] Boveri,[16] Deicher [17] and others.

It is not possible at the present time to determine with certainty whether infectious mononucleosis has appeared in epidemic form. Reports of epidemics previous to the establishment of the serologic test appear in some cases to be definite. Epidemics apparently of this disease have usually occurred among children, in whom symptoms were especially mild. A review of the forty-eight cases that we have encountered shows that for the most part these were clearly sporadic. Exceptions have occurred, however. One patient (case 39), a physician, had infectious mononucleosis clinically on Feb. 23, 1935. This was confirmed by a blood smear and by agglutination and adsorption tests. Thirty-two days later the wife (case 41) of this patient had the disease, as proved by clinical, hematologic and serologic investigations. Retrospective analysis revealed a probable contact occurring either thirty-two days before or within seven days of the onset. Simultaneously, however, with the first case, a third member of the family, a son 2 years of age, had an illness consisting of an acute infection of the upper respiratory tract, fever and cervical adenitis, all of which were of short duration. Although it was not practicable to make confirmatory tests, this was presumably a case of mild infectious mononucleosis. The fourth member of the family, a girl 5 years of age, had a similar illness with the onset occurring several days after that of her brother. Unfortunately, confirmatory tests were not made in her case either. Epidemiologically the train of events suggested serial transmission of the disease through the two children to the mother, thus indicating infection by contact.

14. Ramsdell, S. G., and Davidsohn, I.: J. Immunol. **18**:473, 1930.
15. Bernstein, A.: J. Clin. Investigation **13**:419, 1934.
16. Boveri, R.: Klin. Wchnschr. **12**:666, 1933.
17. Deicher, H.: Ztschr. f. Hyg. u. Infektionskr. **106**:561, 1926.

SUMMARY

Sheep cell agglutinins in the serum of persons with infectious mononucleosis appear to be different from those in normal serum and those in the serum of persons with serum sickness.

The sheep cell agglutinins in normal serum are adsorbed by guinea-pig kidney but not by beef cells; those in the serum of persons with infectious mononucleosis, by beef cells but not by guinea-pig kidney, and those in the serum of persons with serum sickness, by both guinea-pig kidney and beef cells.

Evidence of infection by contact in cases of infectious mononucleosis is given.

E. G. E. Anderson of the Charles V. Chapin Hospital assisted in this work.

COPPER AND IRON IN HUMAN BLOOD

IV. NORMAL CHILDREN

ADOLPH SACHS, M.D.
AND
VICTOR E. LEVINE, M.D.
OMAHA
AND
A. APPELSIS FABIAN, M.D.
NEW YORK

In previous studies [1] of the copper and the iron content of the blood of adults in normal and in various pathologic states we have noted the important interrelationship which exists between these two elements. Especially interesting is the hypercupremia that accompanies anemia. Using the iron content of the blood as a means of estimating the hemoglobin content, we have demonstrated that hypoferronemia is associated with hypercupremia. We have extended our investigation to the blood in infancy and childhood. The present study encompasses an attempt to establish the normal ranges of copper and iron which are necessary for the proper interpretation of the changes in the blood in this age period.

METHODS

The determinations of copper and iron were made during the months from September to December.

Venous blood was drawn from the sagittal sinus of patients less than 1 year of age and from the cubital vein of older subjects.

Blood of the new-born was obtained from the umbilical cord. We have included the five cases previously reported in a comparison of maternal and fetal blood [2] and the blood of another new-born infant. In each instance delivery was spontaneous.

The older subjects were chosen from a group of children at the St. James Orphanage, in Omaha, who had been examined and found to be in good health.

Blood counts were made with standardized pipets and counting chambers of blood drawn by cutaneous puncture of the great toe or of the lobe of the ear.

Determinations of copper were made on 5 cc. samples of blood by a method previously described.[1]

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From the Department of Medicine, Creighton University School of Medicine.

1. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood: I. Normal Men and Women; II. Blood Copper and Iron in Men and Women with Various Pathologic Conditions, Arch. Int. Med. **55**:227 and 241 (Feb.) 1935.

2. Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood: III. Blood Copper and Iron in Pregnancy and in the New-Born, Arch. Int. Med. **55**:249 (Feb.) 1935.

Values for Copper and Iron in the Blood of Normal Children

Name	Sex	Age	Erythrocytes	Copper, Mg. per 100 Cc.	Iron, Wet Ashing, Mg. per 100 Cc.	Iron, Dry Ashing, Mg. per 100 Cc.	Hemoglobin,* Gm. per 100 Cc.
1.....	M	New-born	.....	0.076	53.45	.....	15.92
2.....	M	New-born	.....	0.071	43.65	.....	13.03
3.....	F	New-born	.....	0.075	50.20	.....	14.99
4.....	F	New-born	.....	0.098	50.00	.....	14.92
5.....	M	New-born	.....	0.089	54.65	.....	16.30
6.....	F	New-born	.....	0.091	58.80	.....	17.55
7. All.....	M	1½ mo.	4,590,000	0.152	34.15	.....	10.18
8. Ste.....	M	2 mo.	4,525,000	0.151	34.80	.....	10.39
9. Mar.....	F	3 mo.	3,365,000	0.150	32.25	32.00	9.63
10. Jos.....	M	3½ mo.	4,790,000	0.186	32.50	.....	9.70
11. All.....	M	7 mo.	3,960,000	0.163	35.10	35.56	10.48
12. Jos.....	F	1 yr.	4,520,000	0.190	38.60	38.80	11.52
13. Joh.....	M	2 yr.	3,875,000	0.211	40.50	39.04	12.01
14. Jes.....	M	2 yr.	3,815,000	0.259	32.60	32.00	9.73
15. Ger.....	M	2 yr.	4,000,000	0.200	44.00	43.96	13.01
16. Art.....	M	2 yr.	4,160,000	0.193	40.90	41.04	12.21
17. Jac.....	M	3 yr.	4,000,000	0.250	40.00	40.00	11.94
18. Rob.....	M	3 yr.	3,750,000	0.188	43.10	43.26	12.87
19. Ell.....	M	3 yr.	4,115,000	0.186	37.00	37.36	11.05
20. Alb.....	M	3 yr.	4,025,000	0.203	37.60	37.20	11.22
21. Mar.....	F	3 yr.	3,940,000	0.182	35.70	36.36	10.66
22. Bil.....	M	4 yr.	4,400,000	0.187	42.20	42.12	12.60
23. Jas.....	M	4 yr.	3,800,000	0.160	43.30	43.32	12.93
24. Jos.....	M	4 yr.	3,615,000	0.185	42.20	41.88	12.60
25. Len.....	F	4 yr.	4,430,000	0.167	40.35	40.00	12.04
26. Pet.....	M	4 yr.	4,025,000	0.177	40.10	39.60	11.97
27. Cat.....	F	5 yr.	3,530,000	0.148	41.15	39.80	12.28
28. Ire.....	F	5 yr.	4,340,000	0.173	41.65	41.68	12.43
29. Rit.....	F	5 yr.	4,100,000	0.181	38.45	38.64	11.18
30. Phi.....	M	5 yr.	3,850,000	0.167	40.50	41.88	12.09
31. Joh.....	M	5 yr.	4,190,000	0.205	43.00	42.90	12.84
32. Joh.....	M	6 yr.	3,815,000	0.175	42.35	42.32	12.64
33. Del.....	F	6 yr.	3,840,000	0.182	42.55	42.12	12.70
34. Ral.....	M	6 yr.	4,350,000	0.158	40.55	40.00	12.10
35. Art.....	M	6 yr.	3,830,000	0.172	37.60	37.56	11.22
36. Ang.....	F	6 yr.	4,230,000	0.169	41.65	41.24	12.43
37. Ire.....	F	7 yr.	4,000,000	0.154	42.00	40.80	12.60
38. Owe.....	M	7 yr.	3,900,000	0.182	39.70	40.00	11.85
39. Flo.....	F	7 yr.	4,540,000	0.214	42.00	42.12	12.60
40. Ric.....	M	7 yr.	4,100,000	0.164	40.80	41.04	12.18
41. Paul.....	F	7 yr.	4,325,000	0.168	39.05	39.20	11.66
42. Vir.....	F	8 yr.	4,575,000	0.160	41.50	41.54	12.39
43. Tho.....	M	8 yr.	4,025,000	0.167	38.30	39.50	11.43
44. Cla.....	M	8 yr.	3,540,000	0.181	37.75	37.45	11.27
45. Hel.....	F	8 yr.	3,680,000	0.166	40.00	40.20	11.94
46. Cat.....	F	8 yr.	3,400,000	0.164	36.90	36.36	11.01
47. Jea.....	F	9 yr.	4,350,000	0.156	40.05	40.00	11.96
48. Nel.....	F	9 yr.	3,680,000	0.165	41.85	42.48	12.49
49. Ann.....	F	9 yr.	3,890,000	0.160	39.35	39.20	11.75
50. Joe.....	M	9 yr.	4,040,000	0.169	39.20	37.20	11.70
51. Dor.....	F	9 yr.	4,080,000	0.148	41.50	41.88	12.39
52. Cha.....	M	10 yr.	3,980,000	0.181	41.85	42.32	12.49
53. Tin.....	F	10 yr.	3,840,000	0.174	41.15	41.00	12.28
54. Kat.....	F	10 yr.	3,850,000	0.175	38.75	38.76	11.57
55. Ton.....	M	10 yr.	4,500,000	0.169	40.50	39 80	12 09
56. Rob.....	M	10 yr.	4,500,000	0.169	42.45	42.76	12.67
57. Joh.....	M	11 yr.	3,800,000	0.141	41.65	41.68	12.43
58. Wal.....	M	11 yr.	3,940,000	0.150	43.85	42.76	13.09
59. Hel.....	F	11 yr.	4,000,000	0.137	40.50	40.80	12.09
60. Don.....	M	11 yr.	4,815,000	0.175	44.65	44.44	13.33
61. Ray.....	M	11 yr.	4,040,000	0.180	43.45	42.96	12.97
62. Lil.....	F	12 yr.	4,060,000	0.178	42.55	42.60	12.70
63. Mik.....	M	12 yr.	4,020,000	0.151	40.65	40.00	12.13
64. Bet.....	F	12 yr.	4,000,000	0.141	41.85	42.32	12.49
65. Ant.....	M	12 yr.	3,940,000	0.166	42.55	41.88	12.70
66. Wil.....	F	12 yr.	4,215,000	0.174	41.65	41.24	12.43
67. Joe.....	M	13 yr.	3,965,000	0.175	43.10	42.32	12.87
68. Mil.....	F	13 yr.	4,350,000	0.162	43.30	43.24	12.92
69. Poe.....	M	13 yr.	4,575,000	0.179	43.65	44.44	13.03
70. Mar.....	F	13 yr.	4,420,000	0.165	42.75	42.76	12.76
71. Gab.....	M	14 yr.	4,050,000	0.133	43.45	44.44	12.97
72. Eul.....	F	14 yr.	4,090,000	0.174	43.85	43.24	13.09
73. Dor.....	F	14 yr.	4,520,000	0.140	39.50	41.24	11.79
74. Vic.....	F	14 yr.	3,770,000	0.163	44.25	44.20	13.21
75. Mar.....	F	14 yr.	3,740,000	0.147	41.30	41.88	12.33
76. Mor.....	F	15 yr.	3,850,000	0.157	44.25	43.72	13.21
77. And.....	F	15 yr.	4,330,000	0.149	42.20	42.12	12.60
Average for new-born.....				0.083	51.79		15.45
Average for infants from 1½ mos. to 15 yrs. of age				0.171	40.51		12.00

* Hemoglobin = $\frac{\text{milligrams of iron in 100 cc. of blood}}{3.35}$ = grams of hemoglobin in 100 cc. of blood.

Determinations of iron were made on 0.5 cc. samples of blood by a modified Wong wet ashing method.[3] The results were checked on 5 cc. samples of blood by a dry ashing method which we have devised.[4]

IRON

The blood in infancy, especially during the first year of life, is characterized by a rapidly changing picture. Instead of a single standard for the hemoglobin content, such as is commonly employed for adults, it is preferable to use a standard curve which reflects the normal variations found in each age period. Several normal curves for hemoglobin have recently been reported from different parts of the world.[5]

There is no absolute agreement in the figures reported by the investigators whose results are included in chart 1. The well nourished patients in Williamson's [5a] series uniformly showed higher hemoglobin levels than the relatively anemic institutional subjects included in Mackay's [5e] report. When one takes into consideration the status of the subjects chosen with regard to birth weight, climatic conditions and social and economic conditions, as well as the differences in the methods used for making the determinations of hemoglobin, the curves all tend to conform to a definite configuration. For instance, all agree on the detail of the sharp decline of the hemoglobin content in the new-born that occurs immediately post partum, which was first described by Leichtenstern.[6] The time-honored explanation for this phenomenon ascribes the rapid hemolysis to a physiologic adaptation on the part of the new-born infant to its extra-uterine environment, where the availa-

3. Sachs, A.; Levine, V. E., and Appelsis, A.: Iron in Human Blood, Arch. Int. Med. **52**:366 (Sept.) 1933.

4. Fabian, A. A.; Sachs, A., and Levine, V. E.: Comparison of Wet and Dry Ashing Methods for Determining Blood Iron, Proc. Soc. Exper. Biol. & Med. **32**:662, 1935.

5. (*a*) Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916. (*b*) Wilke, E.: Ueber den Gehalt des Blutes gesunder Kinder vom zweiten bis vierzehnten Lebensjahr an roten Blutkörperchen, an Blutfarbstoff, an Retikulocyten und an Thrombocyten, Folia haemat. **52**:291, 1934. (*c*) Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life, Am. J. Dis. Child. **46**:990 (Nov.) 1933. (*d*) Kotikoff, I. A.: Blood Iron in Nurslings in Normal and Pathologic Conditions, Jahrb. f. Kinderh. **132**: 180, 1931. (*e*) Mackay, H. M. M.: The Normal Hemoglobin Level During the First Year of Life: Revised Figures, Arch. Dis. Childhood **8**:221, 1933. (*f*) Elvehjem, C. A.; Peterson, W. H., and Mendenhall, D. R.: Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **46**:105 (July) 1933. (*g*) Drucker, P.: Investigations on the Normal Values for the Hemoglobin and the Cell Volume in the Small Child, Acta pædiat. **3**:1, 1923. (*h*) Katō, K., and Emery, O. J.: Hemoglobin Content of the Blood in Infancy, Folia haemat. **49**:106, 1933.

6. Leichtenstern, O.: Untersuchungen über den Hämoglobulingehalt des Blutes in gesunden und kranken Zuständen, Leipzig, F. C. W. Vogel, 1878.

ble oxygen is at a higher tension. Horváth and Hollósi [7] have recently demonstrated that polycythemia and an elevated hemoglobin level are not present in infants delivered by cesarean section and in those subjected to a minimum of trauma during labor. Further study may clarify this problem and perhaps modify the accepted views.

Although our series of determinations includes but six infants in the age group from birth to 1 year, we have charted the figures because they coincide with the results obtained by other investigators who have reported representative groups of figures for infants in this age period. Our data conform with the precipitous drop in the hemoglobin curve

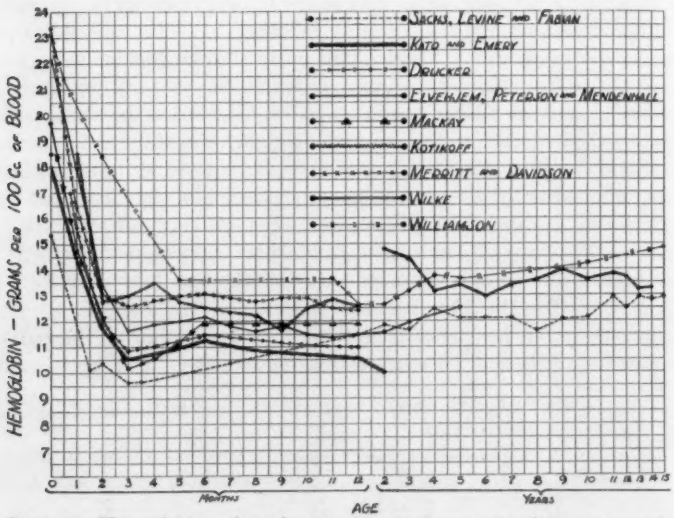

Chart 1.—Hemoglobin values for the blood of normal children reported by various authors.

observed by others in infants in the third month of life. This secondary decline in the hemoglobin content is even less well understood than the original drop occasioned by postpartum hemolysis. Is this a phenomenon due to a depletion of iron? If so, the condition should be amenable to treatment with prophylactic doses of iron administered soon after birth.

The infant relies on its store of blood-building elements to supplement the anemia-favoring milk diet of the first year of life. In premature infants the immediate administration of hematopoietic stimulants is imperative, since the opportunity to store these essentials has been

7. Horváth, Z., and Hollósi, C.: Birth Pains and the Blood of the New-Born, Am. J. Dis. Child. **49**:689 (March) 1935.

denied in utero. The low hemoglobin values during the third month of life of a full term infant may represent either a depletion of the hematopoietic reserve or that point at which the adjustment is finally made in digestive and absorptive processes to insure utilization of the extrinsic supply of hematopoietic requirements.

After the first year of life the figures for hemoglobin show nothing unusual other than a gradual rise to the level for adults. Differences in hemoglobin values due to sex are not observed until after adolescence. The substantial difference in the average figures for the iron content for normal men and women necessitates the establishment of a separate standard for each sex.

We maintain that in children the use of a standard hemoglobin curve is preferable to a single standard. However, for clinical purposes, where percentage figures are in common use, a single standard must be set to represent 100 per cent hemoglobin. The figures for whole blood iron used to estimate the hemoglobin content demonstrate the need for a standard assigned specifically to children. Excluding the iron values for the new-born, the series of seventy-one specimens of blood listed in table 1 gives an average of 40.51 mg. per hundred cubic centimeters of blood. This represents the 100 per cent value for iron in infancy and childhood, which may be included in the following formula:

Milligrams of iron in 100 cc. of blood $\times$ 2.5 = hemoglobin—for children

Our average for a large series of normal men, 50 mg. of iron, and our average for normal women, 45 mg. of iron, per hundred cubic centimeters of blood, were incorporated in the following formulas:

Milligrams of iron in 100 cc. of blood $\times$ 2 = hemoglobin—for men

Milligrams of iron in 100 cc. of blood $\times$ 2.25 = hemoglobin—for women

Therefore, separate standards should be used for men, women and children.

Using the Butterfield [8] factor, iron = 0.335 per cent hemoglobin, the average for the seventy-one children in the present series was 12.09 Gm. of hemoglobin per hundred cubic centimeters of blood. In other words, a normal child would register only 80 per cent hemoglobin on the ordinary clinical hemoglobinometer, which uses one standard for comparison of all bloods regardless of the age or sex of the subject. Hemoglobinometers should be equipped so that the standard can be adjusted in dealing with men, women or children.

8. Butterfield, E. E.: Ueber die Lichtextinktion das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zuständen, Ztschr. f. physiol. Chem. **62**:173, 1909.

Although the iron method for hemoglobin determination has been recommended for its accuracy by many hematologists, some investigators challenge its use. Van Vyve,[9] who first reported a series of blood iron figures for the new-born, listed low values which showed no correlation with hemoglobin percentages as determined by one of the methods in use at the time. Tagliamuro[10] reported similar results. The figures of Halfer[11] did not bear out the proportionality of blood iron to hemoglobin. Sobel and Drekter[12] found in 88 per cent of their cases that the iron method gave hemoglobin values from 5 to 15 per cent lower than those read on a Sahli hemoglobinometer.

With regard to those investigations carried on a few decades ago, one may justifiably question the accuracy of the methods employed for the determination of iron. In the more recent reports the discrepancy may be due to the use of clinical colorimetric hemoglobinometers which are not instruments of precision. Karshan and Freeman[13] compared the method for the determination of iron with the accepted oxygen capacity method for the determination of hemoglobin and found a close correlation of the figures obtained by the two procedures. Abt's recent report on blood iron in children likewise showed that a true proportionality exists between the amounts of iron and hemoglobin.[14]

In our previously reported studies of the iron content of human blood we employed a modified Wong wet ashing process. Burmester,[15] in his comparison of various iron methods, stated that the Wong procedure is not as well controlled as other related technics. We have had an opportunity in our present study to check the results obtained by the Wong method with a dry ashing process on a blood sample ten times as large. After the copper had been removed from the ash of a 5 cc. sample of blood, the precipitate that remained was analyzed for its iron content. The figures obtained by the wet and dry ash methods listed in

9. Van Vyve, G.: Le fer dans le sang des nouveau-nés, Thèse de Paris, no. 415, 1902.

10. Tagliamuro, P.: Contributo clinico-sperimentale sul contenuto in ferro del sangue dei bambini in condizioni normali e patologiche, Pediatria **15**:561, 1907.

11. Halfer, G.: Blood Iron in Children in Normal and Pathologic Conditions, Arch. de méd. d. enf. **33**:659, 1930.

12. Sobel, I. P., and Drekter, I. J.: Determination of the Iron Content of the Blood in Children, Am. J. Dis. Child. **45**:486 (March) 1933.

13. Karshan, M., and Freeman, R. G., Jr.: Study of Hemoglobin Methods, J. Lab. & Clin. Med. **15**:74, 1929.

14. Abt, A. F.: Anemia of Premature Infants: II. A Comparative Study of Blood Iron and Hemoglobin Values in Premature Infants, Am. J. Dis. Child. **49**:1204 (May) 1935.

15. Burmester, B. R.: An Investigation of a Method for Iron Determination in Blood, J. Biol. Chem. **105**:189, 1934.

table 1 showed close agreement. The percentage deviation for the whole series was about 1 per cent. This justifies the use of the rapid wet ash method for iron determination.

COPPER

On the basis of the copper level in the blood of adults, 132 micrograms and 131 micrograms per hundred cubic centimeters of blood for normal men and women, respectively, the blood of the new-born by comparison showed hypocupremia. In the six cases included in table 1 the average value for blood from the fetal cord was 83 micrograms of copper per hundred cubic centimeters, or slightly more than one half the values for adults. We have previously attempted to assign an explanation for these findings.[2]

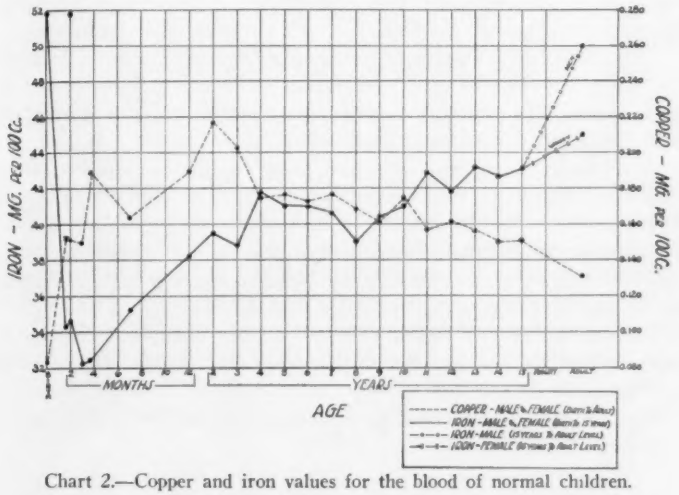

Chart 2.—Copper and iron values for the blood of normal children.

The copper content of the blood begins to rise immediately after birth, reaching a peak during the second year and gradually declining to the level for adults. The average for the seventy-one subjects, aged 1½ months to 15 years, was 171 micrograms of copper per hundred cubic centimeters of blood. This represented a distinctly higher level than that observed for adults. The figures for children, as in the case of those for adults, showed no variation due to sex.

The importance of establishing the normal copper range for children is apparent from an analysis of our previous data for adults. We have observed hypercupremia in anemia and in various other pathologic states. Were the normal standards for adults applied to children, the figures for the children would be designated hypercupremic. A reciprocal rela-

tionship of copper to iron has been observed in human blood. Since the level of the iron in the blood of children is 20 per cent lower than that in adults, the relationship is apparently maintained in the child, who presents a relatively hypercupremic picture. Further graphic evidence of this reciprocal relationship is noted in chart 2. The original hypocupremia of the new-born is associated with hyperferronemia. The trend of figures for each element is then observed to follow in an inverse pattern. The peak for blood copper is accompanied with a relatively low blood iron content. This is followed by a gradual approach of each element to the level for adults.

SUMMARY

The average iron content of the blood of the new-born in six cases was 51.79 mg. per hundred cubic centimeters. The average hemoglobin content for this group was 15.45 Gm. per hundred cubic centimeters.

The average iron content of the blood of seventy-one normal children aged from 1½ months to 15 years was 40.51 mg. per hundred cubic centimeters. The average hemoglobin content for this group was 12.09 Gm. per hundred cubic centimeters.

A separate hemoglobin standard must be set for children if the figures are expressed on a percentage basis. The formula milligrams of iron in 100 cc. of blood $\times$ 2.5 = hemoglobin is suggested as a means of estimating the hemoglobin content of the blood of children.

The average copper content of the blood of the new-born in six cases was 83 micrograms per hundred cubic centimeters.

The average copper content of the blood of seventy-one normal children aged from 1½ months to 15 years was 171 micrograms per hundred cubic centimeters.

Copper and iron maintain a reciprocal relationship in the blood of normal children.

Progress in Internal Medicine

PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE AND A CRITICAL REVIEW OF SURGICAL TREATMENT

GEORGE W. SCUPHAM, M.D.
Assistant Professor of Medicine, Northwestern University Medical School; Attending Physician, St. Luke's and Cook County Hospitals

AND

GÉZA DE TAKÁTS, M.D.
Associate Professor of Surgery, University of Illinois College of Medicine; Attending Surgeon, St. Luke's and Research and Educational Hospitals

CHICAGO

A REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. SCUPHAM

Since the publication of the review of the subject of peripheral vascular disease a year ago there have appeared a large number of papers. Many of them have been reiterations of previous work which, while adding but little new information, have served to clarify the subject and to confirm or contradict conclusions previously offered. Many such contributions are included, and it is hoped that all those which are particularly significant have been considered, although no attempt has been made to include all the papers on the subject.

THE BLOOD VESSELS

In regard to the structure of the capillaries, Jones [1] is of the opinion that fundamentally they are no different from other blood vessels. They have an endothelial layer, a contractile system which consists of smooth muscle cells and a nerve supply. He differs from most previous observers in that he considers that the Rouget cells are not part of the contractile system but an essential part of their innervation.

Capps,[2] by means of the Hewlett and Van Zwaluwenburg plethysmograph, has demonstrated the existence of tone and has studied some

1. Jones, Tudor: The Structure and Mode of Function of the Capillary Blood Vessels, Am. J. Anat. **56**:227, 1936.

2. Capps, Richard B.: A Method for Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand with the Results in Normal and Diseased States, J. Clin. Investigation **15**:229 (March) 1936.

of its characteristics in the small vessels of the hand. He accepts as a definition of tone a resistance to stretch. The tone of these vessels as a group responds to a change of temperature as applied directly and locally. It is increased with a lower temperature and decreased at a higher one. In addition, the response can be demonstrated reflexly by the application of heat to the leg in the manner of Landis and Gibbon. It is to be noted that when the sympathetic nerve supply to the arm was interrupted there was an increase of blood flow into the hand. There was a marked decrease in the tone of the vessels with the local application of heat under such conditions, but there was no reflex response to the application of heat to the legs.

Capps showed that under all conditions, except after interruption of the sympathetic supply, there was a reflex vasoconstriction in these vessels to a noxious stimulus such as a pinch. This confirms the existence of smooth muscle walls with a definite nerve supply to the capillaries, venules and veins unless such an effect is entirely arteriolar.

In regard to the nerve supply, Kuntz [3] suggests an explanation for the failure to secure complete sympathetic paralysis in the upper extremity by extirpation of the inferior cervical ganglion and the first and second thoracic segments of the sympathetic trunk, including the second thoracic ganglion. He believes that there may be a sympathetic pathway within the spinal canal and suggests that small branches recurrent from the gray rami passing into the vertebral canal, which have been considered as terminating in the walls of blood vessels within the canal, may in fact extend along through the vascular plexuses and eventually unite with the brachial plexus. This has not been anatomically demonstrated in human beings but has been observed in cats.

Woollard [4] has a somewhat different explanation for the difference in the results of sympathectomy in the upper and in the lower extremities. He believes that normally the lower extremities have a much greater degree of constrictor tone. He bases this opinion on the observation that anesthetization of the nerves of the legs results in a greater rise in temperature than when the same procedure is carried out on the arms and hands. If the legs are placed in hot water, the skin of the hands quickly shows a rise of temperature; while when the arms are immersed a much longer time is required for a similar rise in surface temperature. Thus, if an increased constrictor tone is an inherent quality of the vessels of the leg, interruption of the nerve control will have less effect in releasing it.

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3. Kuntz, Albert: The Autonomic Nervous System: Essential Anatomy, J. A. M. A. **106**:345 (Feb. 1) 1936.

4. Woollard, H. H.: The Peripheral Sympathetic Nervous System, Brit. J. Surg. **23**:425, 1935.

Scott,[5] in discussing arterial spasms, says that he believes that in extreme forms of increased vasoconstrictor tone which are distinctly abnormal the angiospasm may be sufficiently severe to result in thrombosis and gangrene. Lewis,[6] in making observations on the effect of ergot on the cock's comb, states that the effect of the drug is a marked constriction of the vessels which is not capable of being released by local warming. The constriction is not sufficient to stop the flow of blood, but after a certain length of time the nutrition of the vessel walls fails, stasis occurs with dilatation and thrombosis follows. The circulation is entirely obstructed, and gangrene results.

Scott [5] believes that arterial spasm may occur with organic disease of the vessel, but he points out that in thrombo-angiitis obliterans, in which increased vascular tonus is frequent and often of high grade, the presence of arterial spasm can well be explained by the fact that the essential pathologic condition is an inflammatory process which includes both the vein and the nerve in their extent as well as the artery. It is because of the nerve irritation that the higher degrees of vascular spasm occur. In contrast to this, in arteriosclerosis the disease is degenerative and involves the arterial wall only. The collateral circulation is not affected by the local arterial disease unless all the vessels are similarly involved. Therefore, spasm is not to be expected, and it does not commonly occur. However, Harris [7] is of the opinion that arteriosclerosis is accompanied with sufficient arterial spasm in some cases to warrant sympathectomy. This is not the usual belief, but that some degree of increased vasoconstrictor tonus may frequently exist is not to be doubted.

Scott [5] also described minor grades of spasm of the Raynaud type in which there is great variation of intensity. There is no evidence to indicate that in persons with this condition Raynaud's disease eventually develops, and no line can be drawn to differentiate conditions of this type from the characteristic Raynaud paroxysm. The cause is obscure, and the complaint is usually of a variable sensitivity of the hands and fingers to cold.

Angiospasm may occur in many types of functional and organic nervous disorders and is variable in its manifestations. This is in corroboration of the observations of others, as reported last year.

5. Scott, W. J. M.: Arterial Spasm in the Extremities, Ann. Surg. **102**:331 (Sept.) 1935.

6. Lewis, Thomas: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning, Clin. Sc. **2**:43, 1935.

7. Harris, R. I.: The Role of Sympathectomy in the Treatment of Peripheral Vascular Disease, Brit. J. Surg. **23**:414, 1935.

There is another group of conditions in which angiospasm occurs consecutive to trauma. There are two main types:

1. Local painful ischemic attacks, as in the Raynaud syndrome, in response to exposure to cold. This may be a reflex phenomenon associated with involvement of large or small nerves in scar tissue. Irritation of a peripheral nerve is the essential factor.

2. Painful osteoporosis or reflex traumatic arthritis. This usually involves the foot. There is an inflammatory-like reaction without infection which is regarded as circulatory in origin and angiospastic in nature, although, as described, the superficial circulation is increased. In roentgenograms the bones show the characteristic mottled osteoporotic appearance, and the cartilage between the small bones disappears. Periarterial sympathectomy gives some relief, but ganglionectomy has been more satisfactory. Some patients respond well to conservative treatment.

SURFACE TEMPERATURE

Bierman,[8] after making a study of the temperature of the surface of the skin, states that this temperature varies with that of the environment, with the temperature of the body (internal heat production) and with the condition of the skin and the structures beneath it. It also varies in different regions of the body at a comfortable environmental temperature. It is lower over superficial veins than over arteries. It is higher over muscles than over bones or tendons and is higher over an active than over an inactive organ. Stout persons have a much lower cutaneous temperature than thin persons. Symmetrical areas usually show a variation of 1 C. or less but occasionally show marked variation under normal conditions.

The surface of the skin of the extremities has a lower temperature than that of the trunk and shows the greatest fluctuation with changes in the environmental temperature. With an increase in the internal production of heat or an increase in the environmental temperature the temperature of the surface of the extremities may reach that of the trunk and head. With exposure to cold it falls much more rapidly than that of the body surface.

By means of rapid and constant changes in the temperature of the surface of the body, the temperature of the interior is kept within narrow limits; there is a continual balancing between heat production and heat loss from the surface. Other factors influencing the temperature are age, changes in metabolism and psychic influences.

The variations when there is fever are of interest. When fever is induced by physical means, the normal temperature gradient disappears,

8. Bierman, William: The Temperature of the Skin Surface, J. A. M. A. **106**:1158 (April 4) 1936.

so that all points tend to reach nearly the same level and the temperature of the surface of the extremities may reach a high level even before the internal temperature is elevated. The temperature gradient may then become reversed.

When the body supplies its own energy to create fever, as in the spontaneous development of fever or with the intravenous injection of typhoid vaccine, the temperature of the toes may remain low or may even fall to lower levels while the internal temperature rises. This is during the period of chill. After the internal temperature has become elevated the surface temperature of the extremities rises and remains elevated during the period of defervescence. For this reason Bierman thinks that when the objective of artificial fever is peripheral vasodilatation, it is more rational to produce fever by physical means, since the initial stage of vasoconstriction is avoided.

This agrees with the observations of Johnson, Osborne and Scupham,[9] who observed the effects of the various methods for the artificial induction of fever by means of the plethysmograph. They also found that for maximum vasodilatation in the fingers it was not necessary to raise the body temperature to the higher levels. Temperatures of from 100 to 102 F. were sufficient when physical methods were employed. In fact, at higher degrees of temperature the vasomotor system became unstable, and the amount of peripheral vasodilatation, as measured by the finger plethysmograph, became variable.

When air heated to 100 F. is applied directly by means of a thermostatically controlled hood to the extremities, the surface temperature of the toes rises to the same level as that of the forehead. If the venous return flow of a normal leg is subjected to obstruction, the temperature of the toes rises much more slowly and does not reach the level of that of the unobstructed leg, and likewise in cases of venous disease the temperature response to direct heating is less than normal. In persons with arteriosclerosis, however, the temperature response of the toes to direct heating may be greater than normal. In persons with thrombo-angiitis obliterans the response may be normal or nearly so, because both arteries and veins may be involved. This observation may be of diagnostic value in making a differential diagnosis, if these findings are corroborated by other observers.

The direct application of cool air to the lower extremities rapidly causes a drop in the surface temperature of the toes. The response is delayed and diminished in the presence of arterial disease.

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9. Johnson, C. A.; Osborne, S., and Scupham, G. W.: Studies of Peripheral Vascular Phenomena: IV. The Effect of Artificial Fever on the Pulse Volume Changes of the Finger, Am. J. M. Sc. **190**:485 (Oct.) 1935.

Youmans, Akeroyd and Frank [10] used observations of the surface temperature to study the changes in circulation in the feet and legs with changes in posture and muscular activity. When a subject stood still there was a definite fall in temperature, which in most cases took place gradually until the minimum was reached. In some cases the fall was irregular or intermittent, and when the recumbent position was resumed a rise was again noted. These changes occurred regardless of the environmental temperature. When one leg was exercised and the other was quiet with the subject in a standing position, the fall in temperature occurred in both legs. The circulatory rate was measured and found to be longer with the subject in the erect posture than reclining, but in the moving leg often shorter than when the subject was reclining and consequently several times shorter than in the resting leg.

Heating of the forearms and hands was accompanied with a rise in the surface temperature of the toes with the subject erect which exceeded the drop in surface temperature which followed quiet standing.

INTERMITTENT CLAUDICATION

The importance of objective methods for the measurement of intermittent claudication has been recognized, and attempts have been made to furnish an accurate method. So far most of these have been on the basis of subjective sensations experienced by the patient.

Kisch [11] has employed a test which he calls a standard exertion test of intermittent claudication. It consists of a maximal bending at the ankle, knee and hip joint, so that the knee rests on the abdominal wall, followed immediately by complete extension of these same joints, the body of the patient being in a horizontal position. This exercise is repeated thirty times a minute. The number of times this standard exercise is performed before pain results is designated as the threshold value for claudication, and it varies greatly in different patients. If the value is high, Kisch assumes that the circulatory defect either is well compensated or has not progressed far; the converse is likewise true. A steady increase or decrease in the threshold value indicates improvement or exacerbation of the circulatory defect.

Realizing the importance of a purely objective method of measurement, Hitzrot, Naide and Landis [12] have devised what appears to be an excellent, reliable and purely objective graphic method of measure-

10. Youmans, J. B.; Akeroyd, J. H., Jr., and Frank, Helen: Changes in the Blood and Circulation with Changes in Posture: The Effect of Exercise and Vasodilation, J. Clin. Investigation **14**:739 (Nov.) 1935.

11. Kisch, F.: Zur funktionellen Diagnostik der Dysbasia (Claudicatio) intermittens, Med. Klin. **32**:273 (Feb. 28) 1936.

12. Hitzrot, L. H.; Naide, M., and Landis, E. M.: Intermittent Claudication Studied by a Graphic Method, Am. Heart J. **11**:513 (May) 1936.

ment. The basis of this method is that fatigue of the contracting muscles consistently precedes the pain of intermittent claudication. The early loss of contractile power or amplitude of contraction in muscle deprived of an adequate blood supply is an objective phenomenon which can be recorded graphically. The apparatus used is ingenious and records the contraction of the muscles of the calf, which are stimulated to contraction electrically at varying rates of stimulation and periods of rest. A definite amount of work is performed at each contraction. The records for normal subjects showed remarkable uniformity, both when the circulation was unimpaired and when it was artificially occluded. Fatigue curves were made for the recorded observations on a group of normal subjects. The pain of intermittent claudication did not appear at any time during the test, although some fatigue of the foot or leg developed in some instances. The amplitude of contraction was found to decrease as much as 50 per cent after a two minute period of rapid stimulation. During slow stimulation the amplitude remained constant. Whatever fatigue developed during periods of contraction disappeared during routine rest periods, and the amplitude of contraction returned almost to the initial amplitude after each standard rest period. Age did not affect the type of record. In persons with general weakness after long confinement to bed there were lower amplitudes and mild sensations of fatigue but not the pain of claudication or the rapid drop of amplitude which occurred in persons with vascular disease. With complete obstruction to the flow of blood, fatigue or pain with loss in amplitude occurred even during slow stimulation. In the succeeding rest period there was no recovery. With more rapid stimulation severe symptoms resulted, with a marked reduction in the initial amplitude and without recovery in the succeeding rest period. At a rate of stimulation of 1 contraction per second intolerable pain developed after a few barely measurable contractions, and it was impossible to continue the test. Symptoms and findings of muscular fatigue disappeared quickly after the blood flow was released. Venous congestion at varying degrees favored the development of fatigue and amplitude. Peripheral dilatation in a normal subject produced little or no change in the fatigue curve.

Patients with arterial disease of the lower extremities were studied, with definite and constant findings in each instance. The same intensity of stimulation produced an initial lower amplitude of contraction than in the normal subject. The amplitude of contraction began to diminish earlier and declined more rapidly. In the routine rest periods the recovery of muscle power was less complete, so that the fatigue curves showed a tendency to have a conspicuous downward slope. The diminution in amplitude was associated with sensations of fatigue and pain, which often became so severe that the test could not be completed.

When vascular occlusion had recently occurred, the severity of the fatigue and pain resembled that in a normal subject in whom the blood flow to the muscles of the calf was completely interrupted by a pneumatic cuff. Improvement in the findings occurred in two patients who were under treatment and who showed definite circulatory improvement. It seems that the principal value of the test will be as a means of measuring the improvement following therapy. In one of the two cases reported treatment was by suction and pressure, and in the other, by the administration of tissue extract. This test will be of considerable value in the differentiation of pain of other types which can be confused with that of intermittent claudication. The authors point out that muscle weakness or atrophy due to other than vascular causes also may produce abnormal curves. A certain amount of cooperation on the part of the patient is necessary for the obtaining of good records.

ARTERIOGRAPHY

Opinions regarding arteriography and its usefulness from a diagnostic standpoint are still somewhat at variance. Baumgartner [13] thinks that arteriography is essential to the diagnosis of obstructive arterial lesions. He emphasizes, as do many others, that the method is particularly important because it permits the estimating of the collateral circulation. It is apparent that his views confirm those of others that arteriography is particularly valuable for determining the site of amputation, as reported last year. Edwards,[14] from his own observations and from those of others, is of the opinion that arteriograms in cases of arteriosclerosis and of thrombo-angiitis obliterans are sufficiently characteristic so that these two arterial diseases may be differentiated. In arteriosclerosis the arteriogram may show complete occlusion of the arterial segments, but in addition it shows eccentric filling defects in the other segments. These vessels show a tortuous course, and the collateral circulation is greatly increased. In a case of thrombo-angiitis obliterans the arteriograms show a varying extent of thrombosis with smooth-walled segments of vessels above the occluded portions. The course of the vessels is less likely to be tortuous, and the collateral vessels, though increased in number, are fewer than in a case of arteriosclerosis.

Allen [15] has continued his observation on arteriography and has reported an arteriographic study of the collateral circulation in cases

13. Baumgartner, J. A.: A Contribution on Arterial Obliteration: The Importance of Arteriography in Surgical Diagnosis and Treatment, Deutsche Ztschr. f. Chir. **244**:339, 1935.

14. Edwards, E. A.: The Arteriographic Comparison of Thrombo-Angiitis Obliterans and Arteriosclerosis, New England J. Med. **213**:616 (Sept. 26) 1935.

15. Allen, E. V.: How Arteries Compensate for Occlusion: An Arteriographic Study of Collateral Circulation, Arch. Int. Med. **57**:601 (March) 1936.

of thrombo-angiitis obliterans. He states that the normal arteriogram, as described last year, is characteristic. The main arteries and their important branches are visualized, and short, small branches are to be seen normally, but the collateral circulation is not marked. The arteriogram of a patient with occlusive arterial disease shows a marked collateral circulation, and it is this compensatory circulation which prevents gangrene in many cases of occlusive disease. Allen describes the chief characteristics of collateral arteries. They have a turning and twisting course. They show variation in size in any selected area and purposeless crossing and recrossing. They often pursue a lateral course and have many anastomoses with each other. He is of the opinion that when arterial occlusion develops the arteries which become the collateral vessels are already in existence but increase in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries. Arteriograms of limbs of living subjects show fewer vessels than arteriograms of amputated limbs. The reason for this, Allen believes, is that many vessels in the living subject may not be actually functioning at the time the arteriogram was made and are only called on to function when the circulatory demands are sufficiently great.

Contiadès, Ungar and Naulleau [16] have studied the effect of various contrast mediums used in arteriography on the walls of the vessels. They conclude that no histologic lesions are produced in the arterial wall with colloidal thorium dioxide or organic iodine compounds. Yet they feel that the use of these substances is not without danger. There is always a decrease in the arterial pressure with the use of thorium dioxide. Vasomotor disturbances are common, particularly arterial spasm. The reactions are extremely variable in different subjects; some persons are sensitive and show marked vasospasm, often with pain, and others show little or no reaction.

THROMBO-ANGIITIS OBLITERANS

In regard to the etiology of thrombo-angiitis obliterans there has been little of importance added during the last year. The effect of tobacco and the part it plays in this disorder are still unsettled.

Trasoff, Blumstein and Marks [17] studied cutaneous reactions in a group of thirty-one proved cases of thrombo-angiitis obliterans. With

16. Contiadès, X. J.; Ungar, G., and Naulleau, J.: Recherches expérimentales sur l'action vasculaire des produits de contraste utilisés en artériographie: Application à l'interprétation et la prévision des accidents de l'artériographie, Presse méd. **43**:1630 (Oct. 19) 1935.

17. Trasoff, Abraham; Blumstein, G., and Marks, M.: The Immunologic Aspect of Tobacco in Thromboangiitis Obliterans and Coronary Artery Disease, J. Allergy **7**:250 (March) 1936.

a large number of tobacco antigens they found that the cutaneous tests showed 16 per cent positive results in the group of thirty-one proved cases. The authors do not believe that the reactions had a definite relationship to the disease but consider that the explanation of the effect of tobacco must be on a pharmacologic and not an allergic basis. They further obtained thirty-four positive results to tests with tobacco in forty-one allergic persons, and they point out that of the hundreds of allergic patients whom they have studied none had thrombo-angiitis obliterans.

Friedlander, Silbert and Laskey [18] studied the effect of the injection of extracts of tobacco on albino rats. The tobacco extract was prepared in Ringer's solution and injected intraperitoneally every day, the amount being gradually increased. Thirty-three of the forty-eight male rats treated with injections of denicotinized tobacco had gangrene of the toes within from five to twelve weeks. None of the twelve female rats treated for from five to eighteen weeks showed this lesion. In ten male animals used as controls no gangrene developed. Primary microscopic studies of the vessels showed an inflammatory process. Six rats were subjected to the daily inhalation of smoke, but only one male animal showed lesions similar to those produced by the extract.

Two interesting points to be seen in this work are, first, that vascular lesions could be produced by the effect of tobacco and, second, that these vascular lesions could be produced only in male animals. Braeucker [19] reports a case of endarteritis similar to that of Buerger in which traumatism was the essential etiologic factor. He believes that there may be a constitutional factor which results in the characteristic picture when injury to the vessel wall occurs. This injury may be inflammatory, possibly related closely to rheumatic fever. In the cases which he reports he thinks the cause of the vascular injury was traumatism.

Rabinowitz and his associates [20] have continued the investigations of the relationship of disorders of lipoid metabolism to thrombo-angiitis obliterans. There are apparently two essential effects which may result from disturbances in the highly complex biochemical reactions of phospholipid metabolism. The first is direct, according to Rabinowitz, in altering the coagulability of the blood so that intravascular clotting results. The second is concerned with the relationship

18. Friedlander, Mae; Silbert, S., and Laskey, N.: Toe Lesions Following Tobacco Injections in Rats, Proc. Soc. Exper. Biol. & Med. **34**:156 (March) 1936.

19. Braeucker, W.: Ueber die Ursache der Arterienentzündungen, München. med. Wchnschr. **82**:1186 (July 26) 1935.

20. Rabinowitz, H. M., and Kah, Joseph: Relationship of Phospholipin Metabolism to Thrombo-Angiitis Obliterans and Its Treatment, Am. J. Surg. **31**:329 (Feb.) 1936.

of lecithin and cephalin in the physiology of muscle contraction and the relationship to intermittent claudication.

They have found the phospholipin content of the blood to be increased in cases of thrombo-angiitis obliterans, and choline appears in large quantities in the urine. The phospholipins are made up of lecithin and cephalin. Choline is the end-product of the metabolism of lecithin. Incidentally, the relative amounts of these substances in the blood were found to be constant. In normal subjects the ratio of lecithin to cephalin was 6:1, while in patients with thrombo-angiitis obliterans it was found to be as low as 2:1. This alteration of the ratio results in a tendency to hemolysis and in addition hastens the coagulation process of the blood. There results intravascular clotting, which is so characteristic of the disease.

The level of the phospholipid substances in the calf muscles of patients with thrombo-angiitis was about half that of the muscles of normal controls. The relationship of these substances to the physiology of muscles suggested that intermittent claudication might be the result of this abnormal state. The belief is expressed that pain of this type is not the result of ischemia but rises directly as the result of muscular exhaustion produced by abnormal muscle metabolism in which creatinine phosphate plays a most important rôle.

This is the substance which supplies the energy for muscle contraction. The authors state that the capacity of muscle cells for work depends wholly on the resynthesis and content of creatinine phosphate in the muscles. The phospholipins supply a considerable proportion of the phosphoric acid which is necessary to form the substances on which the physiology of muscle contraction depends. It is to be noted that an adequate supply of oxygen is necessary for this process. Cephalin speeds up the oxidation process. The rate is both absolutely and relatively increased in the plasma in cases of thrombo-angiitis obliterans, and consistently low oxygen values for the venous blood were found, leading the writers to believe that excessive oxidation occurs in the tissues. Because of this a deficiency of oxygen rapidly develops with exercise. The resynthesis of glycogen from lactic acid is impaired, and the typical picture of muscle fatigue and intermittent claudication develops. There was found to be a direct relationship between the deficiency of oxygen in the venous blood and the severity of pain.

To complete the cycle of biochemical reactions, a theory is advanced which increases the importance of phospholipid metabolism. Creatinine is derived from choline, which is also derived from the phospholipids. The energy for this reaction is dependent in turn on the glycogen-lactic acid reaction. The large amount of choline found in the urine may then

be due to the failure of the completion of the cycle of biochemical reactions in the metabolism of muscle contraction.

McGrath,[21] in studying experimental peripheral gangrene, used the method of Rothlin and Polak. Gangrene was produced in the tail of the albino rat by the use of toxic doses of ergotamine tartrate. The gross phenomenon consisted of successive changes in color, including pallor, cyanosis and gangrene. Microscopically the most marked change was proliferation and swelling of the intima. This was particularly marked in the small arterioles and arteries, where in some sections the lumens were almost completely occluded. To a lesser extent the veins and large ventral artery of the tail were involved. In this artery the presence of a thrombus attached to the intima was characteristic. Leukocytic reaction in the arteries and arterioles was not appreciable, but in the veins there were areas of marked thrombophlebitis. The walls of the veins, the thrombus and the perivenous tissues were all involved in an intense infiltration of polymorphonuclear leukocytes. No sex differences were revealed in the original experiments. Male rats were not protected from gangrene by the administration of estrogenic substance. In female rats, however, to which adequate doses of estrogenic substance were given gangrene did not develop under the same experimental conditions. McGrath feels that this curious phenomenon suggests the possibility that the failure of thrombo-angiitis obliterans to become manifest in the female may be associated with a protective action of the estrogenic substance in the internal secretion of the ovary.

Yater and Cahill [22] reviewed the literature on ergot poisoning and report the case of a man, aged 94, to whom ergotamine tartrate had been given for the treatment of pruritus. Gangrene of the feet developed which necessitated amputation. The cause of the gangrene was found to be occlusion of the medium-sized arteries, the small arteries and the arterioles by severe constriction and thrombosis. Intimal proliferation may also play a rôle. The picture in this case was typical of ergot poisoning and did not resemble that of thrombo-angiitis obliterans.

Gould, Price and Ginsberg [23] report the case of a middle-aged woman who received a total dose of 1 mg. of ergotamine tartrate subcutaneously. Coldness and pain developed in the legs, followed by a bluish mottling in the lower two thirds of the legs. Pulsations in the peripheral arteries

21. McGrath, E. J.: Experimental Peripheral Gangrene, J. A. M. A. **105**:854 (Sept. 14) 1935.

22. Yater, W. M., and Cahill, J. A.: Bilateral Gangrene of the Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice, J. A. M. A. **106**:1625 (May 9) 1936.

23. Gould, S. E.; Price, A. E., and Ginsberg, H. I.: Gangrene and Death Following Ergotamine Tartrate (Gynergen) Therapy, J. A. M. A. **106**:1631 (May 9) 1936.

disappeared. Death occurred several days later. The essential observation, in addition to arteriosclerosis, was of marked arteriolar constriction.

Pathology.—Lindenbaum and Kapitza [24] are of the opinion that migratory phlebitis always accompanies thrombo-angiitis obliterans. It frequently precedes arterial involvement, and these authors think that the intensity and the spread of the inflammation in the veins indicate the severity of the process in the arteries. They divide the disease into three stages: stage 1, migratory phlebitis without symptoms or with irrelevant symptoms of involvement of the arteries; stage 2, migratory phlebitis with definite arterial impairment, and stage 3, migratory phlebitis with widespread thrombosis of the peripheral arteries.

The pathologic condition in the veins in the first stage consists of a fresh thrombus, with an inflammatory reaction in the wall, perivascular edema and leukocytic cellular infiltration. Small granulomatous nodules in which necrotic foci may appear begin to develop. Later, organization takes place in the thrombus. It is suggested that these granulomatous nodules are sometimes difficult to differentiate from tubercles. They contain large cells which become vacuolated and often contain fat as well as polymorphonuclear giant cells. A second type of focal reaction occurs in the thrombus itself with the formation of epithelioid giant cells and lymphocytic infiltration. This phase is followed by organization. The thrombus becomes infiltrated with lymphoid cells and histiocytes. The process goes on to obliteration of the lumen or recanalization, as in cavernous angioma. In some of the resected veins no thrombus was present, only a thickening of the intima which encroached on the lumen.

Jáki,[25] on the other hand, does not believe that thrombophlebitis migrans is always linked with thrombo-angiitis obliterans. He believes that an infection of low virulence is the cause and that it is of the nature of an allergic reaction in which latent and infectious foci are most important. He prefers the term thrombophlebitis saltans to the one usually used. It seems apparent that other types of migratory phlebitis occur in addition to that associated with thrombo-angiitis obliterans.

Friedlander, Laskey and Silbert [26] made observations on the blood volume of twenty-five patients who had undergone surgical removal of

24. Lindenbaum, I., and Kapitza, L.: Zur Klinik und pathologischen Histologie der Buergerschen Form der Thrombo-Angiitis obliterans, Arch. f. klin. Chir. **184:** 413 (Jan. 22) 1936.

25. Jáki, J.: Ueber Thrombophlebitis migrans (saltans) und ihre Aetiologie, Zentralbl. f. Chir. **62:**2056 (Aug. 31) 1935.

26. Friedlander, Mae; Laskey, Norman, and Silbert, S.: Studies in Thrombo-Angiitis Obliterans (Buerger): X. Reduction in Blood Volume Following Bilateral Oophorectomy, Endocrinology **19:**461 (July-Aug.) 1935.

the ovaries and uterus. A number of female cats were subjected to removal of both ovaries. The average blood volume following operation showed a reduction of about 25 per cent from that of normal controls. There was an elevation of the cholesterol and fibrinogen contents of the plasma and an increase in the viscosity of the blood. The authors believe that some substance capable of influencing the blood volume is produced by the ovaries even after other physiologic functions have ceased. The cats subjected to operation likewise showed a tendency to a reduction of blood volume.

ARTERIOSCLEROSIS

Duff [27] has written an exhaustive review of the subject of experimental cholesterol arteriosclerosis. He concludes that in rabbits and guinea-pigs cholesterol is responsible for the atherosclerotic changes which follow the feeding of this substance. It has not been possible to obtain the same effect in other animals. The characteristic sclerotic changes are preceded by preliminary alteration in the vessel walls which are probably dependent on the cholesterol feeding. It is in these areas that the lipoid deposits occur and the characteristic alterations take place. Hypercholesteremia and saturation of most of the viscera with cholesterol also occur. This disease, he believes, is not identical with arteriosclerosis in man. There are three essential factors in the development of experimental cholesterol arteriosclerosis: (1) cholesterol in the diet, (2) hypercholesteremia and (3) injury to the intima of the arteries. He states that there is no valid reason for believing that hypercholesteremia is noted regularly in association with arteriosclerosis in man. There is no evidence that a disturbance of the lipoid metabolism participates in the etiology. The initial stage in the development of human arteriosclerosis consists of local changes in the walls of the arteries which are responsible for the subsequent deposits of lipoid material. These changes follow some sort of injury to the vessel wall, the cause of which is not known. After the initial local injury lipoids are deposited in the damaged intima, especially in the intercellular substances. Macrophages engulf the lipoid material. The free lipoid deposits probably stimulate the proliferation of connective tissue in the intima, and this effect plus the original injury produces a reparative fibrotic process. The lipoid deposits may prevent immediate healing, and consequently the lesions persist and progress. In some instances the lipoids may slowly absorb and finally disappear, leaving only a fibrinous thickening of the intima.

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27. Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**:81 (July); 259 (Aug.) 1935.

Meeker, Kesten and Jobling [28] studied the effect of iodine on experimental cholesterol arteriosclerosis in rabbits. Potassium iodide in large doses was fed for from one to three months to rabbits in which atherosclerosis had previously been induced by the prolonged feeding of cholesterol. It was found to have no effect on the rate or nature of the involution of the vascular lesions, but it did appear to retard the return of the cholesterol content of the blood to normal levels. The authors suggest that this retardation may be due to the mobilization of stored cholesterol from the tissues.

Blotner [29] reports a case of diabetic arteriosclerosis in which gangrene developed. It is his opinion that the excessive use of tobacco was the final factor in the precipitation of gangrene in this case and suggests that when the circulation is sufficiently impaired in cases of arteriosclerosis the excessive use of tobacco should be prohibited.

Sprague,[30] in a discussion of the etiology of arteriosclerosis in man, holds that in spite of the many objections that have been raised against the validity of experimental arteriosclerosis one cannot escape the fact that this demonstration is a most significant step, in that atherosclerosis has actually been produced and in its production has shown some analogy with the arterial degeneration so frequent in diabetes mellitus, in which a disturbance of cholesterol metabolism is a factor. Other foods, including alcohol, he believes, play no part unless excesses in diet may be of some importance. Tobacco likewise is not considered a factor. He notes that arteriosclerosis in youth and middle age is predominantly a disease of males. Of twenty-five patients 40 years of age or younger who had coronary thrombosis, all were men. Sprague finds a plausible theory for this and speculates on the possibility of an unknown endocrine factor. While hypertension may lead to vascular degeneration it cannot be considered the etiology of arteriosclerosis. That there are racial and possibly hereditary factors which result in premature vascular disease seems certain. The author concludes that no theory of the etiology is wholly satisfactory and that the cause of degenerative vascular disease is unknown. However, the boundaries of the problem are being progressively narrowed by the study of experimental arteriosclerosis and by the chemical analysis of the vessels, as well as by studies of the properties of colloidal gels and by studies in human biology.

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28. Meeker, D. R.; Kesten, H. D., and Jobling, J. W.: Effect of Iodine on Cholesterol-Induced Atherosclerosis, Arch. Path. **20**:337 (Sept.) 1935.

29. Blotner, Harry: Excessive Smoking as a Possible Precipitating Factor in Diabetic Gangrene, with a Case Report, Ann. Int. Med. **9**: 987 (Jan.) 1936.

30. Sprague, Howard B.: The Etiology of Degenerative Vascular Disease, New England J. Med. **213**:659 (Oct. 3) 1935.

Beck, Fowler, Koenig and Bowen [31] state that vascular disease is common in obese persons and a frequent cause of death in such subjects. They found that the calcification of the arteries of the lower extremities was demonstrable roentgenographically. This is an exceedingly common finding in older persons with uncontrolled diabetes, but in persons in the early stages of diabetes and in obese persons, some of whom are potential diabetic patients, it is essentially absent. There is no essential difference pathologically between the sclerosis that occurs in the older diabetic patients and that in persons with senile atherosclerosis.

ACUTE ARTERIAL OCCLUSION

Millar and Reid [32] have written an excellent review on the subject of embolism, including pulmonary as well as peripheral embolism. It is useless to attempt a review of this paper here.

McKechnie and Allen [33] have made a study of one hundred cases of embolism and thrombosis of the peripheral arteries at the Mayo Clinic. They do not differentiate entirely between thrombosis and embolism. They comment on the fact that pain is not the constant symptom which it usually is thought to be. It was frequently absent in their group of cases. In only 54 per cent of the cases was pain the initial symptom. Numbness, coldness and tingling were common, and loss of muscle power was occasionally prominent. Heart disease was the usual cause of embolism, while thrombosis most frequently resulted from arteriosclerosis. The cessation of symptoms may indicate eventual recovery or gangrene. When gangrene was definitely established the symptoms were less severe. In some cases in which gangrene did not develop the initial symptoms gradually merged into those of ischemic neuritis. The chief physical findings were absence of pulsation of the acral arteries, lowering of the surface temperature, pallor and loss or diminution of the reflexes, sensation and muscular strength. The pallor was of an unusual degree. Thrombophlebitis was the only condition which was considered to cause difficulty in making a diagnosis. The prognosis in this group of cases was not good. Gangrene developed in from 45 to 50 per cent of the cases. As the study of this group of patients dated back to 1924, the outcome for the entire group is not comparable to that for

31. Beck, E. C.; Fowler, J. G.; Koenig, E. C., and Bowen, B. D.: Vascular Disease in the Obese Diabetic and in Non-Diabetics: A Discussion of Arteriosclerosis as a Cause of Diabetes, Ann. Int. Med. **9**:662 (Dec.) 1935.

32. Millar, W. M., and Reid, M. R.: Present-Day Views on Embolism, Internat. Abstr. Surg. **61**:505 (Dec.) 1935.

33. McKechnie, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities: A Study of One Hundred Cases of Embolism and Thrombosis, Proc. Staff Meet., Mayo Clin. **10**:678 (Oct. 23) 1935.

groups of patients who have the benefit of modern methods of treatment. Thrombosis, particularly that due to arteriosclerosis, seems to produce lesser degrees of gangrene than embolism. Treatment should be initiated promptly. The use of local heat, particularly uncontrolled heat, such as the use of a hot water bottle, is dangerous because tissue deprived of its normal blood supply tolerates excessive heat poorly. Opiates should be used for the control of pain, and alcohol is an important and valuable drug. The limb should be protected from the slightest injury, and the temperature of the air should not exceed 105 F. The authors advise the use of papaverine hydrochloride intravenously in amounts of ½ grain (0.03 Gm.). Improvement will follow within a few minutes if this drug is effective. General or spinal anesthesia may be used in selected cases for securing maximum peripheral vasodilatation. The use of intermittent negative and positive pressure is also advised but will be discussed later.

McIlhenny and his associates [34] emphasize the necessity for accurate, early diagnosis and the prompt institution of treatment.

Clute [35] reports two cases of acute arterial obstruction resulting from arteritis. Following the point of view of Leriche, he states that in cases of acute arteritis some signs and symptoms will develop which are due to the loss of blood supply and others will appear because of constant stimulation of the vasomotor sympathetic nerve fibers in the artery. Acute arteritis may arise during the course of an overwhelming general infection, such as septicemia or pneumonia. This type of arteritis is usually a terminal event. It may occur also, as in the two cases reported, as a localized arterial infection in the arterial wall. Focal infection may be the etiologic factor. Trauma is another factor which needs consideration. The onset of symptoms of acute arteritis is gradual. Weakness of the extremity is worse after exercise and is often an early symptom. The limb becomes cold and may become blanched. Cyanosis and excessive sweating may be noted. On examination pulsation in the involved artery is absent, and the vessels can be felt as a cord which is sometimes tender. Blood pressure readings are not obtainable. Changes in sensation, atrophy of the muscles and trophic ulcers may occur. Pathologic study following resection of a portion of the vessel in some cases showed periarteritis with thrombosis. Smears and cultures revealed no significant observations. Early operative treatment with resection of a portion of the artery is recommended; this procedure was successful in both the cases reported.

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34. McIlhenny, R. A.; McIlhenny, R. C., and Voldeng, K. E.: Embolism of the Extremities, J. Kansas M. Soc. **16**:450 (Nov.) 1935.

35. Clute, Howard M.: Acute Arterial Obstruction from Arteritis, New England J. Med. **214**:137 (Jan. 23) 1936.

SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

Periarteritis nodosa is being reported with increasing frequency. Middleton and McCarter [36] have recently reported three cases, in males. This sex predominates in all reports. The age incidence covers a wide range—from 3 months to 71 years. The authors believe that the incidence of the disease clearly exceeds its clinical and pathologic recognition. It seems to be closely associated with the group of rheumatic diseases.

Bernstein [37] describes a case of periarteritis nodosa without peripheral nodules, diagnosed by biopsy. The patient's illness was characterized by weakness, emaciation, fever, peripheral neuritis, abdominal pain, edema, amblyopia, tachycardia, eosinophilia and changes in the urine. The author comments on the fact that the disease is probably not as uncommon as the cases reported on indicate.

Volland [38] describes a case in a woman, aged 61, who had a syphilitic aortic aneurysm. The small arteries of all the organs showed the picture of periarteritis nodosa; in addition, atypical amyloid degeneration occurred in the media and adventitia of the small arteries and in the cardiac muscle. Volland questions the relationship of this disease to syphilis and considers the possibility of an allergic etiology.

Knauer [39] describes the case of a patient who died of pulmonary tuberculosis and who had an abdominal aneurysm. The typical picture of healed periarteritis nodosa was demonstrated in the lung. The author is of the opinion that syphilis had nothing to do with the arterial disease.

Mainzer and Joël [40] report a typical case of periarteritis nodosa which began as an infection of the throat. During a course of three years Streptococcus viridans was present in blood cultures, and it was noted also at autopsy. The authors believe this to be a streptococcic infection. Motley [41] has described a case in which the important features were generalized involvement of a somewhat migratory character involving the vessels of both the upper and the lower extremities, the skeletal muscles and the kidneys, with symptoms of coronary disease, severe abdominal pain, bloody diarrhea, peripheral neuritis and cough with blood-streaked sputum. There was marked leukocytosis and an

36. Middleton, W. S., and McCarter, J. C.: The Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190**:291 (Sept.) 1935.

37. Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. **190**:317 (Sept.) 1935.

38. Volland, W.: Periarteritis nodosa mit atypischer Amyloidose nach luischer Infektion, Beitr. z. path. Anat. u. z. allg. Path. **96**:81 (Nov. 18) 1935.

39. Knauer, Bernhard: Ueber einen Fall von vollkommen abgeheilter Periarteriitis nodosa, Centralbl. f. allg. Path. u. path. Anat. **63**:161 (Aug. 30) 1935.

40. Mainzer, F., and Joël, W.: Periarteritis Nodosa as a Manifestation of Sepsis Lenta Due to Streptococcus Viridans, Acta med. Scandinav. **85**:397, 1935.

41. Motley, L.: Periarteritis Nodosa, J. A. M. A. **106**:898 (March 14) 1936.

eosinophil count as high as 28 per cent. The diagnosis was made during life, and the patient was treated with repeated blood transfusions, small doses of neoarsphenamine, a diet rich in vitamins and general symptomatic measures. There was apparent recovery.

Krahulk, Rosenthal and Laughlin [42] report an additional case, in which the widespread vascular lesions of necrotizing panarteritis occurred in a girl aged 9 years. The unusual feature in this case was subacute leptomeningitis.

Barker and Baker [43] describe another type of obscure arteritis under the term of proliferative intimitis of the small arteries. The outstanding clinical features that are mentioned in connection with this case are marked livedo reticularis, recurrent indolent ulceration, acute occlusion of the small arteries of the toes and severe intractable pain. Extensive proliferation of the intima and definite perivascular fibrosis in many of the small arteries and veins were noted. In some of the vessels the lumen was closed with a fibrous mass. Associated with this was marked periarterial fibrosis. This seemed to be a late stage of the disease. Many of the arterioles had thick walls with small lumens surrounded by irregular areas of fibrous tissue. There was no evidence of tuberculosis or syphilis, and the authors were unable to suggest any etiologic agent.

RAYNAUD'S DISEASE

Just where the line can be drawn between the typical Raynaud paroxysm and the so-called vasomotor neurosis of the same type is impossible to determine. Certainly many of the vasomotor neuroses, especially those precipitated by cold or emotion, although not typical of Raynaud's disease, are disorders of the same type. Although these minor disorders never seem to progress, their etiology is no more definite than that of Raynaud's disease.

Peet and Kahn [44] have published reports on a group of patients exhibiting vasomotor phenomena which they feel were allied to the Raynaud syndrome. In all cases there was evidence of organic disease. In one patient there was a tumor of the hypothalamus, which they believe was the cause of the vasomotor disturbance. The second patient showed a constant vasoconstrictor spasm involving both legs. This was relieved by ganglionectomy. Microscopic examination of the ganglion showed inflammatory reaction in the cells and other evidences of chronic

42. Krahulk, L.; Rosenthal, M., and Laughlin, E. H.: Periarteritis Nodosa (Necrotizing Panarteritis) in Childhood with Meningeal Involvement, Am. J. M. Sc. **190**:308 (Sept.) 1935.

43. Barker, N. W., and Baker, T. W.: Proliferative Intimitis of the Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis and Recurring Necrotic Ulcers of the Skin, Ann. Int. Med. **9**:1134 (Feb.) 1936.

44. Peet, Max Minor, and Kahn, Edgar A.: Vasomotor Phenomena Allied to Raynaud's Syndrome, Arch. Neurol. & Psychiat. **35**:79 (Jan.) 1936.

inflammation. The authors cite the case of another patient, reported by Bennet and Poulton, who had vasomotor paroxysms in the hands that were typical of Raynaud's disease. Autopsy later revealed a large carcinoma of the stomach, and examination of the inferior cervical ganglion, removed at operation, revealed carcinomatous metastases. In the third case described by Peet and Kahn there were definite vasomotor changes in the legs and hands—both abnormal vasoconstriction and vasodilatation. The definite lesion of the spinal cord, which was a meningocele, was removed at operation. Apparently complete cure resulted. In the fourth case fracture of the skull resulted in extensive cortical injury, and there were marked vasomotor disturbances which consisted of symmetrical cyanosis involving the trunk. For a short distance below the cyanosed area the skin was completely blanched. These observers believe that it is probable that in some cases of the Raynaud syndrome the smooth muscle of the smaller blood vessels has abnormal irritability. Further, it is thought that in some cases so-called typical Raynaud's disease may be caused by the same factors which underlie hysteria. The authors' final conclusion is that Raynaud's disease is merely a syndrome, since it can be caused by an exciting factor, pathologic or functional, located anywhere from the cerebral cortex throughout the various nerve pathways and even in the peripheral vessels themselves. The cases described are not of Raynaud's disease but of typical vessel spasm resulting from central or peripheral nerve irritation.

Kraetzer [45] advances the unique idea that the retention of arsenic in the body in certain cases may be the toxic factor responsible for Raynaud's disease. In proof of this he cites seven cases of a more or less typical Raynaud syndrome in which retention of arsenic was demonstrable. Six of these were in females and one in a male. There was an increase in the urinary output of arsenic in all of them following the intravenous injection of sodium thiosulfate. This was the only treatment instituted, and after its continuation for a variable period all the patients showed relief from symptoms and marked improvement in the general health. The history of the onset of symptoms was variable; usually syncope of one or more fingers ushered in the complaint. Later the spasm in almost all cases became widespread and in many of them was typical of the Raynaud paroxysm.

Johnson and Hedges [46] studied the circulation in a case of Raynaud's disease complicated by scleroderma and sclerodactylia. Their conclusions

45. Kraetzer, Arthur F.: Raynaud's Disease: An Hypothesis as to Its Cause, New York State J. Med. **35**:1 (Nov. 15) 1935.

46. Johnson, Carl A., and Hedges, Robert N.: Studies on Peripheral Vascular Phenomena: IV. Finger Volume Changes in a Patient Showing Raynaud's Phenomena, Surg., Gynec. & Obst. **60**:1077 (June) 1935.

were as follows: The circulation was persistently less than normal in the fingers even in the absence of paroxysm. Peripheral dilatation can be induced by the local application of heat, and during the cyanotic stage of these paroxysms the circulation is increased. The use of insulin-free pancreatic extract resulted in improvement in the color of the fingers but did not produce vasodilatation.

Pearse [47] found that in cases of Raynaud's disease, even when the hands were kept warm, cooling of the body caused the appearance of a paroxysm. Warming the body relieved the attack, but the converse also was true. Warming the body did not prevent an attack if the hands were exposed to cold. The author concluded that regulation of the body heat has a definite effect on the paroxysm of Raynaud's disease. This is confirmatory evidence that normal forms of stimulation produce an exaggerated vascular reaction. The local abnormality causes the excessive spastic response from a number of diverse motivating factors.

ACROCYANOSIS

Concerning the subject of acrocyanosis relatively little interest has been aroused. This is no doubt due to the fact that this disorder causes little or no disability; in fact, many persons who have the disorder make no complaint of their symptoms.

Elliott, Evans and Stone [48] made a careful study of one case of unusually severe acrocyanosis and made observations on two cases in which the symptoms were milder. Their conclusions as to the fundamental vascular defect are at variance with those of Lewis and Landis, but the authors agree in some respects. The larger arteries, including the digital arteries, were found to be intact, as were the larger veins. These authors disagree with Lewis and Landis that arteriolar constriction is the essential defect. They are convinced that there are a loss of tone and a loss of normal reactivity to stimulation of the small superficial vessels of the skin, namely, the capillaries and the collecting venules. The authors agree, however, that arteriolar constriction resulting from exposure to cold will intensify the symptoms by diminishing the inflow to the superficial vessels. The arguments that they have advanced are convincing. However, it does not seem reasonable that acrocyanosis, as they think, should not be regarded as a disorder that is secondary to disease elsewhere in the body, as almost all previous workers have considered it to be.

47. Pearse, H. E., Jr.: Influence of Heat Regulatory Mechanism on Raynaud's Disease, Am. Heart J. **10**:1005 (Dec.) 1935.

48. Elliott, A. H.; Evans, R. D., and Stone, C. S.: Acrocyanosis: A Study of the Circulatory Fault, Am. Heart J. **11**:431 (April) 1936.

Capps [2] studied acrocyanosis in two cases with a plethysmograph. An abnormal absence of tone of the capillaries, venules and veins was noted. His findings are in agreement with those of Elliott, Evans and Stone that this loss of tone in the vessels on the venous side coupled with a slow arterial inflow at low temperatures is probably the explanation of the clinical features of the disorder.

ERYTHROMELALGIA

Mühlbächer [49] describes erythromelalgia as occurring in healthy men and women in attacks of burning pain at night, usually in the feet, lasting for a few hours and ceasing only to return again the next night. It seldom occurs during the day. Its cause is some disturbance for which no pathologic basis can be demonstrated in the vasomotor system, in the cerebral centers or in the ganglions. Elevation and rest afford some relief. Many types of treatment have been employed, but they are usually temporarily helpful, the symptoms sooner or later recurring. The author has tried insulin-free pancreatic extracts and the intravenous injection of calcium with some benefit. Ergotamine tartrate in small doses in combination with belladonna also is advised. Nothing further has been added to clarify this obscure condition.

EFFORT THROMBOSIS

Effort thrombosis has been reported in the last year with increasing frequency from many sources. That it is a definite clinical entity cannot be doubted, although the exact reason that thrombosis develops is still obscure. Little has been added to the clinical picture previously described. While in most of the cases the condition has involved the axillary vein or other veins of the upper extremities, Kux [50] reports four cases of traumatic thrombosis of the leg. These were all the result of direct trauma or excessively strenuous work. The clinical picture was the same in all cases. Swelling of the extremity, with paresthesias, coldness, fatigue and bluish-red discoloration was outstanding. The superficial veins presented a cordlike appearance. The author divides the condition into two types. The first is a purely thrombotic type and results from a tear or injury to the intima of the vein. In the second type, which he believes is due to overexertion, thrombosis follows as the result of hindrance to the flow of blood. Rossel [51] states that the arm is most often affected, particularly the arm which is more frequently

49. Mühlbächer, W.: Ueber Erythromelalgie und deren Behandlung, München. med. Wchnschr. **82**:1242 (Aug.) 1935.

50. Kux, E.: So-Called Traumatic Thrombosis in the Arm and Axillary Vein, Beitr. z. klin. Chir. **161**:286, 1935.

51. Rossel, E.: So-Called Traumatic Thrombosis of the Axillary Vein, Svenska läk.-tidning. **126**:935, 1935.

used. Effort thrombosis occurs in young persons with good muscular development. The author thinks the prognosis is good under conservative treatment.

Robinson [52] describes two cases of primary thrombosis resulting from excessive muscular effort which involved the thoraco-epigastric artery of the right side. In one patient the condition developed after he had been digging in the garden, and in the other after he had moved some heavy furniture. The symptoms were pain in the side of the chest and the presence of a firm, tender cord. A stringlike band could be felt under the skin running up from the costal margin and disappearing in the axilla. Robinson believes the thrombosis to be the result of injury to the intima of the vein during the contraction of the underlying muscles. It is possible that axillary thrombosis may originate in this vein, the primary thrombosis being overlooked because of the major condition affecting the axillary vein.

McClanahan [53] reports the case of a muscular boy of 17 years. He points out that the initial attack may be somewhat mild but that continuation of the use of the arm will result in much more severe involvement. The arm should be allowed to rest until adequate circulation has been established.

Veal and McFetridge [54] have reported two cases of primary thrombosis of the axillary vein. The clinical history corresponds to that usually described. Venography in these cases revealed the location of the obstruction clearly, and in a case in which the obstruction had existed for a long time there was an extensive collateral circulation. The authors believe the cause to be trauma plus some anatomic predisposing factor. Hyperabduction and external rotation of the shoulder seem to be important factors. Obstruction usually occurs where the vein crosses the subcapularis muscle.

TREATMENT

In the treatment of peripheral vascular disease the principal advances in the past year have been the correlation and crystallization of ideas and the application of the various methods more definite to each type of disease. It has again been emphasized that peripheral vascular

52. Robinson, R. H. O. B.: Thrombosis Following Strain, Brit. J. Surg. **23**:241 (Oct.) 1935.

53. McClanahan, B. V.: Primary Thrombosis of the Axillary Vein, Am. J. Surg. **30**:459 (Dec.) 1935.

54. Veal, J. R., and McFetridge, E. M.: Primary Thrombosis of the Axillary Vein: An Anatomic and Roentgenologic Study of Certain Etiologic Factors and a Consideration of Venography as a Diagnostic Measure, Arch. Surg. **31**:271 (Aug.) 1935.

disease is a local manifestation of a general disease. Barker [55] again asserts that in spite of the many warnings the vulnerability of the toes of patients with occlusive arterial disease has not been sufficiently emphasized. Gangrene is induced by the most trivial type of injury. In 35 per cent of a series of one hundred and seventy-one cases of thrombo-angiitis obliterans with gangrene, this condition followed various therapeutic procedures, while in 39 per cent of one hundred and fifteen cases of arteriosclerosis with gangrene, therapeutic procedures were the cause. The author strongly recommends that no local, surgical or medical treatment of the toes be instituted in any case until the arterial blood supply has been proved adequate.

De Takáts [56] in a report of five cases of acute arterial occlusion states that striking improvement in the circulation often follows the intravenous use of papaverine hydrochloride. If this drug is to be of any benefit it must be given as soon as the diagnosis of pulmonary or peripheral embolism is made. The intravenous injection of papaverine is a harmless procedure and can be available at all times, whereas other methods of treatment are often impossible outside of a well equipped hospital. As previously reported, the effect is prompt if any benefit is to be obtained. No stable solutions of papaverine are available. The author points out that the drug can be kept on hand in capsules and that solutions can be quickly made and sterilized by boiling. The principal effect of combating the reflectoric vessel spasm of arterial occlusion deserves the widest recognition. In embolism of the peripheral vessels papaverine used in combination with controlled heat and negative pressure has given excellent results.

Acetyl-beta-methylcholine is reported on again by Grace Goldsmith,[57] who states that it has three important actions: a parasympathetic stimulating effect, a vasodilating effect and a nicotine-like effect, which causes a rise in the blood pressure when its other actions have been abolished by atropine. Schwab and his associates [58] state that although primarily exerting its effect on the craniosacral division of the vegetative nervous system, it also produces vasodilatation of the peripheral arterioles, presumably by inhibition of the sympathetic constrictors. These investigators considered the possibility that this effect is due to stimulation of the parasympathetic vasodilator fibers, provided such fibers exist.

55. Barker, N. W.: The Danger of Gangrene of the Toes in Thrombo-Angiitis Obliterans, J. A. M. A. **104**:2147 (June 15) 1935.

56. de Takáts, Géza: The Use of Papaverine in Acute Arterial Occlusions, J. A. M. A. **106**:1003 (March 21) 1936.

57. Goldsmith, Grace A.: The Effectiveness of Acetyl-B-Methycholine Given by Mouth as a Vasodilating Agent, Ann. Int. Med. **9**:1196 (March) 1936.

58. Schwab, Edward H.; Marr, W. L., and Moore, Robert M.: Clinical Studies on the Action of Acetyl-Beta-Methylcholine Chloride, Texas State J. Med. **31**: 574 (Jan.) 1936.

Goldsmith studied the effects of the oral administration of the drug and found a rise in the temperature of the skin to be usual. This rise was greatest in cases of hypertension and of Raynaud's disease. In cases of these conditions doses of 50 mg. were often effective, whereas in cases of arteriosclerosis and thrombo-angiitis obliterans from 1,000 to 1,500 mg. was needed to produce significant vasodilatation. There was marked variability in the rise of the surface temperature in the various digits in cases of Raynaud's disease. In one case the rise in the temperature of the fingers varied from 1.9 C. (3.5 F.) in one digit to 8.9 C. (16 F.) in another. Organic occlusion of smaller vessels was thought to be the reason for this variation. Patients with hypertension and control subjects showed a uniform rise in temperature in all the digits. The action of the drug began from fifteen minutes to two and one-half hours following its oral administration. The duration of the rise in cutaneous temperature varied from one to six hours. By giving another dose of 1,500 mg. in three or four hours vasodilatation could be maintained for seven or eight hours. In three cases of thrombo-angiitis obliterans a comparison was made with the vasodilating effect of typhoid vaccine given intravenously. Acetyl-beta-methylcholine was found to have 75 per cent of the vasodilating effect of artificially induced fever. The administration of this drug failed to relieve any of the severe grades of pain in cases of occlusive disease of the blood vessels, nor was any definite effect noted in cases of intermittent claudication. The effect on the pulse rate and the blood pressure when the drug was given by mouth was variable and not significant, in contrast to the effects of the subcutaneous administration, after which the blood pressure, heart rate, sweating, salivation and nausea were often increased.

Goldsmith concludes that this drug seems to be promising for use in cases of peripheral vascular disease because of its vasodilating properties, its prolonged action, the safety in its use and the ease of its oral administration. It seems, however, that its principal use may be found in Raynaud's disease or other conditions in which there is marked spasm of the smaller arteries. Schwab and his associates [58] agree in this. They found striking increases in the temperature in cases of Raynaud's disease. Some of the digits showed a rise of as much as 10 C. (18 F.), with pronounced systemic relief.

McGovern, McDevitt and Wright [59] studied the effect of theobromine with sodium salicylate as a vasodilator. They concluded that this drug is unreliable and too feeble a vasodilator to be useful in the treatment of peripheral vascular disease.

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59. McGovern, Teresa; McDevitt, Ellen, and Wright, Irving S.: Theobromine Sodium Salicylate as a Vasodilator, J. Clin. Investigation **15**:11 (Jan.) 1935.

Lehman [60] has applied elevation of the environmental temperature in one case of acute arterial spasm. He suggests that this may have definite therapeutic possibilities.

Samuels' [61] monograph on the diagnosis and treatment of peripheral vascular disease is limited to a discussion largely of thrombo-angiitis obliterans. The author again emphasizes the value and describes in detail the technic of treatment with hypertonic solutions of sodium chloride.

Silbert [62] has reviewed his experience of ten years with the treatment of thrombo-angiitis obliterans by intravenous injections of hypertonic solution of sodium chloride. There is no essential change in his views, and certainly the results which he has obtained have been gratifying.

The center of interest in peripheral vascular disease during the past year has been in treatment with positive and negative pressure. There is still no unanimity of opinion in regard to the usefulness of this method under all conditions. The original workers have apparently had much more success than have others. Herrmann,[63] in an excellent monograph recently published, describes the history of various methods of treatment with positive and negative pressure over the past hundred years and their development to the present state. He describes in detail the application of this plan of treatment of the various types of vascular disease and gives an excellent résumé of other methods of treatment, together with the physiology and pathology of vascular diseases. Reid and Herrmann [64] state that the most startling results have been obtained among patients who are suffering from more or less sudden occlusion of the major arterial pathways to an extremity. The results in the treatment of the acute crises of peripheral vascular accidents have been the most thrilling observation in their clinic for many years. In every instance of acute obliteration of a major artery in which there was no obvious death of tissues, they were able to relieve the spasm and draw blood into the extremity in a short time, with quick relief from pain and

60. Lehman, Edwin P.: A Suggestion for Simple Treatment of Acute Arterial Spasm, Am. J. M. Sc. **190**:459 (Oct.) 1935.

61. Samuels, Saul S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1936.

62. Silbert, Samuel: Thrombo-Angiitis Obliterans (Buerger): XI. Treatment of Five Hundred and Twenty-Four Cases by Repeated Intravenous Injections of Hypertonic Salt Solution; Experience of Ten Years, Surg., Gynec. & Obst. **61**: 214 (Aug.) 1935.

63. Herrmann, Louis G.: Passive Vascular Exercises and the Conservative Management of Obliterative Arterial Diseases of the Extremities, Philadelphia, J. B. Lippincott Company, 1936.

64. Reid, Mont R., and Herrmann, Louis G.: Non-Operative Treatment of Peripheral Vascular Diseases, Ann. Surg. **102**:321 (Sept.) 1935.

the prevention of gangrene. This, they say, has been accomplished even when sensation in the extremity was absent or markedly diminished.

The value of this method of therapy, in their experience, diminishes when occlusion of the arterioles occurs unassociated with sudden increases in the pathologic process and consequently is not complicated by vasospasm. Whenever the occlusive processes outbalance the ability of the collateral vessel to furnish adequate arterial blood and also upset the normal, delicately adjusted vasomotor mechanism, this form of therapy forms a most valuable adjunct. In cases of thrombo-angiitis obliterans the authors admit the method to be much less effective, and they think that considerable care and judgment are necessary in its use for treatment of this condition. This is especially true when there is acute migratory phlebitis or when intense rest pain exists. If the inflammatory process is exceedingly active pavaex therapy may do harm. A spread of inflammation may result, and intense pain may follow. In the quiescent phases of the disease, when the thrombo-inflammatory processes have subsided, pavaex therapy has been beneficial. In patients with peripheral arterial sclerosis associated with diabetes, the arteriolar bed is usually fairly good, and pavaex therapy has been effective even in the presence of ulceration, infection and gangrene of the toes. When these conditions exist it must be used with discretion, and the amounts of pressure must be varied according to the condition of the patient.

Herrmann [65] states that the permanency of the collateral circulation developed by this method is dependent on the nature of the disturbance. The increase in circulation brought about in patients with arteriosclerosis has often increased in magnitude until a definite and efficient circulatory balance has been produced. In conjunction with passive vascular exercise the author has employed local artificial hyperthermia with encouraging clinical results. The local application of heat increases the local metabolism of the tissues, with a consequent increased demand for arterial blood. If the arterial circulation can be increased in proportion to the increase in the demand for blood, reconstructive processes should take place more rapidly. The degree of local hyperthermia during passive vascular exercises should be from 104 to 106 F. It is applied by supplying preheated air to the interior of the boot. The use of this procedure is particularly valuable in the presence of moist, spreading gangrene in which the arteriolar pathways of the extremities are impaired.

Herrmann [66] has shown by arteriographic studies of patients treated by passive vascular exercises an enormous increase in the size and

65. Herrmann, Louis G.: The Management of Organic Peripheral Vascular Diseases, Wisconsin M. J. **35**:185 (March) 1936.

66. Herrmann, Louis G.: Non-Operative Treatment of Inadequate Peripheral Distribution of Blood: Passive Vascular Exercises and Local Hyperthermia, J. A. M. A. **105**:1256 (Oct. 19) 1935.

number of useful collateral arteries in the distal parts of an extremity which has been treated intensively. Pulsations in vessels have returned, and calorimetric and oscillometric studies have demonstrated conclusively, in his opinion, that the collateral circulation brought about by this means remains active for many months after treatment is discontinued. It is obvious that the degree to which collateral arterial circulation can be developed depends largely on the actual number of arteriolar and small arterial pathways that are open and not involved by the disease process.

The use of hyperthermia in conjunction with passive vascular exercise overcomes the peripheral vascular spasm that accompanies the active types of obliterative arterial disease and thus helps to surmount one of the most important obstacles to the formation of a sustained collateral circulation. Hyperthermia finds important application also in combination with passive vascular exercises in the treatment of arteriosclerosis obliterans with or without gangrene and with or without associated diabetes. Feet that had been subject to various degrees of freezing responded promptly, and serious sequelae were prevented in all the cases in which this method of treatment was given.

The observations of Landis and Hitzrot [67] on suction and pressure therapy are in essential agreement. They feel that it is a worth-while addition to other conservative methods for the treatment of peripheral vascular disease. Good results can be obtained even when organic obstruction has advanced to the stage in which the arterial blood flow can no longer be increased by methods depending on vasodilatation. They found that both the subjective and the objective phenomena of ischemia can be relieved after conservative measures have failed. They also feel that the method is of particular service in increasing the local blood flow, at least temporarily, during episodes of pain or ulceration, so that time may be gained for the development of an adequate collateral circulation. They emphasize several contraindications and point out that it is necessary to investigate the extremity before each treatment, particularly when there are open lesions, to make sure that phlebitis has not developed and that infection is not spreading. A slight elevation of temperature should be an indication to proceed with extreme caution. Treatment should be discontinued in the presence of encapsulated pus. The authors conclude that therapy of this type should be applied with caution and in selected cases. They point out that the treatment should not be left in the hands of a technician but should be under the definite supervision of a physician.

67. Landis, E. M., and Hitzrot, L. H.: Treatment of Peripheral Vascular Disease by Means of Suction and Pressure, Ann. Int. Med. **9**:264 (Sept.) 1935.

Krusen [68] has described a modification of the apparatus of Landis and Gibbon. It seems as if this might be somewhat more convenient for general clinical use, but fundamentally it shows no important differences. Allen and Brown,[69] after using the Herrmann and Reid apparatus, are much less optimistic as to the result secured. They comment on the fact that in their hands this method of treatment has not produced any results that they had not observed repeatedly following simpler methods. They feel that good results are obtained with suction and pressure management in those cases in which good results could be expected from other measures, and that when good results do not follow other measures suction and pressure treatment is usually without value. Particularly in cases of thrombo-angiitis obliterans they believe the intravenous injection of typhoid vaccine is so good that this other type of treatment cannot be compared with it. According to their observations suction and pressure treatment and increases of the cutaneous temperature may relieve pain and induce the healing of ulcer. The pain of ischemic neuritis is definitely relieved. They state that the greatest therapeutic need is a satisfactory method of treating older patients with the occlusive arterial lesions of arteriosclerosis. They feel that passive vascular exercise has been of no particular help in this direction.

Conway [70] has reported on the use of the Herrmann and Reid apparatus. He states that in his opinion this therapeutic measure has justified its inclusion in medical therapeusis. He agrees that the method is physiologically sound, and in nine of ten cases of sudden vascular occlusion the treatment was effective. There was improvement in more than 80 per cent of the cases of arteriosclerosis obliterans, and in four cases of thrombo-angiitis obliterans no benefit was derived. Conway found no evidence that this method of treatment was harmful in any case. Wilson and Roome [71] reported the results of twenty-three cases in which treatment was by this method. Their findings in cases of thrombo-angiitis obliterans were essentially the same as those of other observers. Six of the eight patients treated showed no benefit, and two showed only slight improvement. They agree that many of the patients felt subjectively improved during the course of the treatment but

68. Krusen, Frank Hammond: Passive Vascular Exercise for Diseases of Peripheral Vessels, Arch. Phys. Therapy **16**:581 (Oct.) 1935.

69. Allen, Edgar V., and Brown, George E.: Intermittent Pressure and Suction in the Treatment of Chronic Occlusive Arterial Disease, J. A. M. A. **105**:2029 (Dec. 21) 1935.

70. Conway, J. Herbert: Obliterative Vascular Disease: Report of Fifty-One Cases Treated With Passive Vascular Exercise, J. A. M. A. **106**:1153 (April 4) 1936.

71. Wilson, Harwell, and Roome, Norman W.: Passive Vascular Exercise: Observations on Its Value in the Treatment of Peripheral Vascular Diseases, J. A. M. A. **106**:1885 (May 30) 1936.

reported no beneficial results when questioned two or more months later. They find it difficult to say whether the beneficial results that followed were to be attributed to this method or to the other measures concurrently employed.

Pfahler [72] has reported on the roentgen therapy of thrombo-angiitis obliterans. He found that irradiation alone over the affected extremity did not produce satisfactory results, but with the proper doses applied over the sympathetic ganglions supplying the parts involved, he obtained excellent results. Pain was often relieved in two or three weeks; intermittent claudication disappeared and circulatory and trophic disturbances were relieved in from two to six weeks. There was an early tendency for moist gangrene to become dry, and the dead tissue gradually separated from the healed area. These results are unusually striking and seem to be important.

SURGICAL TREATMENT: A CRITICAL REVIEW

By Dr. de Takáts

Contributions published since our last review can again be most conveniently grouped as dealing with (1) attempts to improve the circulation, (2) attempts to relieve pain and (3) methods of amputation.[73]

VENOUS LIGATION

An explanation of the therapeutic effect of ligation of the concomitant vein in cases of arterial obstruction is attempted by Bell.[74] He points out the rise of venous and capillary pressure and the increase of filtration pressure over the osmotic pressure when a vein is tied. In the extremity afflicted by arterial obstruction the hydrostatic pressure in the capillaries falls below the osmotic pressure. There may be enough blood in the minute vessels; but circulation will not take place from the capillaries to the tissues, and nutrition is seriously impaired. Venous ligation restores the normal relationship between the hydrostatic and the osmotic pressure by raising the former and thus may be a temporary aid to circulation.

This principle may be successfully employed when ligation of a larger artery becomes necessary. As stated in our previous review, ligation of a concomitant vein has not been of definite benefit in cases of chronic vascular disease of the extremities.

72. Pfahler, G. E.: Roentgen Therapy of Thrombo-Angiitis Obliterans (Buerger's Disease), Am. J. Roentgenol. **34**:770 (Dec.) 1935.

73. No attempt is made to offer a complete bibliography. Articles have been selected which contain new trends of thought or bring a well founded challenge to prevalent ideas, thus constituting progress in vascular surgery.

74. Bell, James: The Ligation of Veins with Arteries, Irish J. M. Sc., June 1935, p. 262.

ARTERIECTOMY

The subject of arterial excision (arteriectomy) is again discussed in two papers from the clinic of Leriche. In an experimental study Fontaine and Schattner [75] found that the blood supply of a hindlimb of a dog is much more impaired when the thrombosed arterial segment is left in place than if an arterial segment of the same length is resected. Not only are there spasm and a slower development of collateral circulation in the presence of a thrombosed artery, but distal to the obstruction there appear endarteritis and mesarteritis or even thrombosis of the blood vessels. No such lesions are found on the arteriectomized side. A clinical report by Leriche and Fontaine [76] is based on eighty cases of arterial excision. The diagnosis was syphilitic arteritis in two cases, Buerger's disease in thirty-four, arteriosclerosis in thirty-four, embolism in four and traumatic thrombosis in four cases. The femoral artery was exposed in most cases, and it was often necessary to resect segments of from 20 to 25 cm. (9 to 11 inches). Arteriography with thorium dioxide was used to localize the obliterated segment. Care must be exercised not to destroy the collateral vessels close to the distal end of the obliterated artery, as they carry blood to the main vessel below the obstruction in the reverse direction.

Clute [35] resected short segments of the inflamed thrombosed brachial artery in two cases; partial relief was obtained in the first and complete relief in the second case. He does not believe that total removal of the involved artery is necessary, as favorable results can be obtained by simply interrupting the continuity of the artery. He makes the interesting suggestion that it may be worth-while to remove a section of the artery when ligation of a major vessel is necessary. The arterial excision, he believes, hastens the formation of collateral circulation by the interruption of the periarterial sympathetic fibers.

We have stated previously that "such an operation is not indicated in the majority of cases of peripheral vascular disease." In the occasional instance of accurately localized segmental thrombosis, such as is encountered in traumatic thrombosis, in localized arteritis and at the site of arterial ligatures, arteriectomy deserves serious consideration. The mechanism of its beneficial action lies in the interruption of afferent sensory impulses activating a sympathetic vasoconstriction through a spinal reflex and not, as Leriche thought, in paralysis of the periarterial sympathetic plexus. Reflexes originating from such occluded arterial

75. Fontaine, R., and Schattner, R.: Les bases expérimentales de l'artériectomie, J. de chir. **46**:849 (Dec.) 1935.

76. Leriche, R., and Fontaine, R.: Conditions necessaires, résultats et technique de l'artériectomie, Presse méd. **43**:1953 (Dec. 4) 1935.

segments can be equally well interrupted by means of paravertebral injections of alcohol or sympathetic ganglionectomy.

EMBOLECTOMY

In a case of acute arterial occlusion [77] an attempt must be made to differentiate between peripheral embolism and acute arterial thrombosis. From the probable site of the occlusion together with the patient's age and cardiovascular status one can estimate the danger of gangrene from occlusion at that particular level. Vigorous conservative measures, including the use of heat, of papaverine and of alternating suction and positive pressure, are worthy of trial. These measures serve the purpose of overcoming the concomitant vascular spasm which occurs with every sudden arterial occlusion. The probable pathways of the reflectoric vasoconstriction are discussed. If these conservative measures fail and if the patient is seen within the first ten hours, embolectomy is indicated. This report is based on ten cases of embolism and twenty-nine cases of acute arterial thrombosis. The author urges a less passive attitude toward peripheral vascular crises, which are still being ignored or treated with indifference.

PARAVERTEBRAL INJECTION OF ALCOHOL

The injection of alcohol into sympathetic nerves was used by Patterson and Stainsby [78] as an excellent substitute for operative procedures. The technic of paravertebral nerve block is described. It requires a thorough anatomic knowledge and many trials on cadavers. In addition to eleven patients with rheumatoid arthritis, the authors treated eight patients with Buerger's disease, and they cite the case of one patient with Raynaud's disease. The authors prefer this form of treatment to protein shock and to peripheral sensory nerve block. They have used the method for ambulatory patients.

It is true that with sufficient experience paralysis of the sympathetic innervation of an extremity can be accomplished by paravertebral injections of alcohol. It must be emphasized, however, that unless temporary results are sufficient, as in cases of acute arterial obstruction, a return of sympathetic activity may be expected. The anatomic variations of the sympathetic chain and ganglions are so great that the percentage of failures must be considerable. Finally, disturbing paresthesias and paralysis may result from injection into an intercostal or lumbar nerve. The method is valuable but requires just as much skill as the surgical exposure and excision of the sympathetic ganglions.

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77. de Takáts, G.: Acute Arterial Occlusions of the Extremities, Am. J. Surg. **33**:60 (July) 1936.

78. Patterson, R., and Stainsby, W. J.: The Therapeutic Effects Following Interruption of the Sympathetic Nerves, Ann. Surg. **103**:514 (April) 1936.

SYMPATHETIC GANGLIONECTOMY

The anatomy of the ganglionated trunk has been the subject of two exhaustive reports. Braeucker [79] studied the lumbosacral trunk in sixty-two cadavers and states that a number of variations exist which are accompanied with changes in the position of the lumbosacral somatic plexuses. There may be from three to six lumbar sympathetic ganglions, and differences on the two sides are frequent. He also observed that myelinated white rami may emerge from the third lumbar ganglion and also from the upper sacral ganglions—a statement contrary to current teaching. Perlow and Vehe [80] have given instructive diagrams of the most frequent variations of the cervicothoracic and lumbosacral chains. Not only do the size and the shape of the ganglions vary, but their relations to vessels and lymph chains and their connections to the somatic plexuses are inconstant. These investigators noted an occasional connection between the second thoracic ganglion and the first thoracic nerve. In nine of forty-eight lumbar cords dissected the lumbosacral cord divided longitudinally. Only four of the forty-eight cords presented a textbook picture of five definite ganglions with medium-sized chains. In only four of twenty-four cadavers did the cords look alike on the two sides.

These observations emphasize that a possible cause of failure following sympathectomy may be incomplete removal of the ganglionated trunk or incomplete severance of communications between sympathetic and somatic outflow. Perlow and Vehe postulate a microscopic identification of the lumbar sympathetic trunk, especially on the left side, where the trunk is surrounded by lymph vessels and glands.

A histologic study of sympathetic ganglions removed in cases of Raynaud's and Buerger's disease, acute bone atrophy and Quincke's edema is reported by Sunder-Plassmann.[81] He noted spotty atrophy, vacuolation, autolysis, chromatolysis in the ganglions and matting of the neurofibrils. In cases of Buerger's disease and Sudeck's atrophy there was in addition a proliferation of the intraganglionic fibrils with neuroma formation. The "mantle cells" around the ganglions were increased in number. Such ganglions send pathologic stimuli or act as multipliers of normal stimuli to the periphery; hence surgical removal is indicated.

Physiologic observations on the sympathectomized limb have added to the better understanding of the effect of this operation. Freeman [82]

79. Braeucker, W.: Die anatomischen und physiologischen Grundlagen der lumbosakralen Sympathektomie, Arch. f. klin. Chir. **183**:636 (Oct. 28) 1935.

80. Perlow, S., and Vehe, K. L.: Gross Anatomy of the Stellate and Lumbar Sympathetic Ganglia, Am. J. Surg. **30**:454 (Dec.) 1935.

81. Sunder-Plassmann, P.: Untersuchungsergebnisse zur Grenzstrangchirurgie, Arch. f. klin. Chir. **183**:653 (Oct. 28) 1935.

82. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and Sympathectomized Limb, Am. J. Physiol. **113**:384 (Oct.) 1935.

showed that after sympathectomy the circulation of the hand is dependent on the metabolic requirements of the tissues. The circulatory stimulus is mediated, as first suggested by Roy and Brown in 1879, through the concentration of metabolites, perhaps their acidity. In the normal hand there is in addition a reflex control in accordance with the needs of the body, so that circulation functions as a part of the heat regulating mechanism. After sympathectomy the blood flow is no longer modified in a thermoregulatory fashion, although epinephrine will exert a strong influence.

From a practical standpoint these important observations indicate that the sympathectomized limb is more independent of thermal influences than the limb not operated on. In case of peripheral vascular disease, reflectoric vasoconstriction is thus abolished.

Other stimuli than cold, such as pain, pressure and noise, and intrinsic stimuli, for instance deep breathing, an altered temperature of the blood, visceral pain and mental activity, are all ineffective in diminishing the digital volume in the sympathectomized limb, whereas the normal reaction to all these stimuli is vasoconstriction, as measured by the diminished volume of the finger.[83] This vasoconstriction is independent of the integrity of the anterior and posterior roots but is dependent on the continuity of both the preganglionic and the postganglionic sympathetic fibers. It is therefore a mechanism the efferent pathway of which is a sympathetic nerve. The interruption of these fibers does not prevent an afferent stimulus from that limb from producing vasoconstriction in the digits of other limbs, but the stimulus will not produce vasoconstriction of the same limb if it is sympathectomized.

These findings seem to be of considerable importance. They mean that if an afferent painful stimulus originates in a diseased blood vessel, such as is encountered in Buerger's disease, it cannot cause reflectoric vasoconstriction in the same limb if it is deprived of its sympathetic nerve supply. These studies may throw light also on the symmetricity of certain vascular lesions in cases in which a painful stimulus of one extremity causes vasoconstriction in the opposite limb.

The mechanism of the decrease in volume of the hand following a standard stimulus (a pinch) has been analyzed by Capps,[2] who observed it to be dependent on an increase of the tone of the veins, venules and capillaries as measured by a decrease in volume. The tone of these vessels increases with cold and decreases with heat, and excessively low or high temperatures abolish the reflex changes in volume. The reflectoric diminution in the volume of the hand can be abolished by sympathectomy.

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83. Stürup, G.; Bolton, B.; Williams, D. J., and Carmichael, E. A.: Vasomotor Responses in Hemiplegic Patients, Brain **58**:456 (Dec.) 1935.

Several papers have included discussions of the surgical approach to the sympathetic chain and ganglions. Flothow [84] has performed approximately one hundred cervicodorsal sympathectomies by the dorsal approach and is dissatisfied with the method. He advocates the anterior approach of Gask, which he has performed five times. He believes that it is possible to obtain exposure as far down as the fifth dorsal ganglion, a possibility which, on the basis of considerable experience with Gask's method, appears to me to be doubtful.

The last word in regard to the most successful approach has not been said, and we are awaiting further progress with interest. For the removal of the stellate ganglion and the dorsal chain as low as the second thoracic ganglion the anterior approach seems satisfactory. But if, as will be discussed later, the optimal sympathectomy for the upper extremity will necessitate section of the trunk below the third ganglion, the posterior muscle-splitting approach may again come into favor.

Telford [85] also has given up the posterior approach to the cervicothoracic ganglion after thirty-five operations because it is more mutilating, because it is followed by a more stormy convalescence and because the exposure of the stellate ganglion is unsatisfactory, as the root of the first thoracic nerve lies between the surgeon and the ganglion. He believes that failures of sympathectomy on the upper extremity may be due to an incomplete technic or the late stage of the disease but that they occur mainly because the usual cervicothoracic sympathectomy produces postganglionic degeneration of the sympathetic fibers and results in sensitization of the denervated vessels to epinephrine. The great significance of this sensitization with regard to recurrences or residual symptoms after sympathectomy has been forcibly brought out by White (see last year's review). To avoid this postganglionic degeneration, Telford cuts the sympathetic trunk below the third ganglion and cuts the second and third white rami. Smithwick and White [86] have developed a method of preganglionic section through a posterior approach. They cut the spinal cord below the third ganglion. In addition, the second and third intercostal nerves are resected for a length of 3 or 4 cm., as far as the intervertebral foramen, so as to interrupt all possible preganglionic rami.

Our limited experience with the preganglionic section of Telford has been most encouraging. The difference between a preganglionic and a postganglionic section is most striking in the same patient. Observations of longer duration will be necessary to determine the lasting

84. Flothow, P. G.: An Adequate Anterior Approach for the Removal of Cervicodorsal Sympathetic Ganglia, West. J. Surg. **43**:589 (Oct.) 1935.

85. Telford, E. D.: The Technique of Sympathectomy, Brit. J. Surg. **23**: 448 (Oct.) 1935.

86. White, J. C.: Personal communication to the author.

value of this method, which represents a clinical application of the important contribution of Freeman, Smithwick and White to surgery of the sympathetic nervous system.

Grant,[87] on the basis of studies on the denervated ear of the rabbit, also comes to the conclusion that if the phenomenon of the regaining of vascular tone after sympathectomy is the same in man as it is in the rabbit, preganglionic section is preferable to ganglionectomy for peripheral vascular disease because it reduces the subsequent reactivity of the vessels. These vessels are increasingly responsive not only to epinephrine but to solution of posterior pituitary, histamine, ergotoxin, faradization and cold. The explanation of this phenomenon is left open. However, the author does not believe that the increased reactivity is due to nerve degeneration. It is apparent from one of his graphs that increased responsiveness of the vessels also develops after preganglionic section, but the vessels do not respond as vigorously as vessels of which the postganglionic fibers have been cut.

According to Woollard,[4] the well known difference between results on the upper and those on the lower limb following sympathectomy is due to the increased constrictor tonus of the lower extremity developed because of the upright posture. In the light of the different responsiveness of vessels to preganglionic and postganglionic sections, however, the explanation of White seems more plausible. He pointed out that lumbar sympathectomy produces a preganglionic section for the majority of the fibers, all except those that go to the femoral and obturator nerves. Thuse the degree of sensitization to epinephrine is much smaller in the lower extremity.

Several new approaches have been described for lumbar sympathectomy. Harris [7] advocates a transverse abdominal incision at the level of the umbilicus, cutting the oblique and transversalis muscles and the fascia of the rectus muscle but not the rectus muscle itself. This is an extraperitoneal approach, permitting the removal of one chain at a time. Rees [88] discusses the objections to previous methods. The posterior approach of Royle requires two operations and gives an unsatisfactory exposure of the lower lumbar ganglions. Adson's transperitoneal approach may be followed by intestinal obstruction and even fatal ileus. Flothow's [89] method requires a two stage operation, and the incision cannot be extended up or downward according to need. Flothow uses

87. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, with Special Reference to the Effects of Denervation, Clin. Sc. **2**:1, 1935.

88. Rees, C. F.: Single Incision, Transabdominal Extraperitoneal Approach to Lumbar Ganglia, Am. J. Surg. **32**:234 (May) 1936.

89. Flothow, P. G.: Anterior Extraperitoneal Approach to the Lumbar Sympathetic Nerves, Am. J. Surg. **29**:23 (July) 1935.

a muscle-splitting incision at the level of the umbilicus. Rees makes a Y-shaped incision in the midline through skin and fat and two longitudinal incisions through the fascia and the inner third of the rectus muscle. The line of cleavage between the posterior sheath of the rectus muscle and the peritoneum having been found lateral to the rectus muscle, the peritoneum is peeled medially, and the chains are exposed on both sides.

As in case of cervicodorsal sympathectomy, the choice of surgical approach is difficult; nor is it likely that one method will suit all conditions. Whether the operation is planned to be unilateral or bilateral and whether the patient is lean or obese will influence the selection of the best type of method. Surgeons actively engaged in surgical intervention on the sympathetic nervous system should be familiar with several of these methods to insure the proper selection in a given case.

Indications for and results following sympathectomy have been discussed by Harris.[7] Four of the seventy-five patients suffered from Raynaud's disease, and in all of them the condition was improved. Rather unusual is his group of twelve patients with peripheral arteriosclerosis, five of whom derived benefit from the operation. Of the patients with Buerger's disease, 58 per cent showed immediate and late benefit, 20 per cent of the operations having been performed too recently to make evaluation of the results possible. The immediate results were good, but amputation had to be performed later in 8.9 per cent, and poor results, meaning no improvement or persistence of rest pain necessitating amputation, were obtained in 12.2 per cent. The author emphasizes the fact that all the patients who showed a marked rise in the cutaneous temperature after nerve block derived benefit from sympathectomy, and sometimes even a patient with a slight rise in the surface temperature showed an appreciable increase in circulation, sufficient to turn the scale from impending gangrene to rapid healing of ulcers and restoration of the ability to undertake a limited amount of work.

Sanchís-Perpiñá [90] advocates sympathectomy for varicose veins, varicose ulcers and trophic ulcers. He produced trophic ulcers by injecting a 50 per cent solution of lactic acid into the lumbosacral ganglions. He leaves the second lumbar ganglion intact and thus does not abolish sweating and pilomotor reflexes. He claims to have obtained good results. It seems that this operation constitutes preganglionic sympathectomy for a large area of the lower extremity but leaves both the preganglionic and the postganglionic fibers to the femoral and obturator nerves intact and is thus an incomplete operation.

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90. Sanchís-Perpiñá, V.: Neue experimentelle und klinische Beiträge zur lumbosakralen Sympathikuschirurgie, Beitr. z. klin. Chir. **161**:442, 1935.

Danielopolu and his co-workers [91] believe that the vasoconstrictor fibers to the hindlimbs of the dog do not pass out to the lumbar nerves or along the aortic plexus. When they stimulated the sympathetic chain above the second lumbar ganglion, they produced vasoconstriction in the hindlimbs. This effect could be almost completely abolished if the sympathetic chain had been transected at the level of the promontorium. When the distal stump of such a transected lumbosacral chain was stimulated, vasoconstriction occurred again. On the basis of these findings the authors advocate resection of the lumbosacral chain at the level of the promontorium. Clinical results on the basis of twenty-five cases have indicated to them that this relatively simple procedure, which can be performed in one stage through a midline transperitoneal approach, is just as efficacious as the much more extensive removal of the lumbar sympathetic chain from the diaphragm to the aortic bifurcation.

The method of Danielopolu obviously resembles that of Sanchís-Perpiñá [90] and can be again interpreted as constituting a preganglionic section of all the sympathetic fibers the cell stations of which are in the sacral ganglions. However, it leaves the fibers to the femoral and obturator nerves intact. These two nerves, with the exception of a small strip of tissue innervated by the saphenous nerve, carry no sympathetic fibers to the foot. My experience with such lumbosacral transection in persons with poliomyelitic extremities indicates that the results are not as good as those following complete lumbar sympathectomy. However, further work along these lines may be well worth while.

W. J. Merle Scott [5] feels that the irritation of sensory fibers around diseased or obstructed vessels is the origin for afferent impulses which cause a marked vasoconstrictor reflex. This vasoconstriction extends not only over the diseased vessel but to the anastomotic and terminal vessels on which the viability of the extremity distal to the obstruction depends. Sympathetic ganglionectomy in carefully selected cases offers the patients the most complete and permanent vasodilatation of the collateral circulation. For the severe types of angiospasm consecutive to trauma, lumbar ganglionectomy has been satisfactory.

This concept of regarding so many of the vasomotor phenomena as an efferent activation of a sensory-sympathetic reflex arc has been most fruitful in many peripheral vascular disorders. It also explains why arterial excision and sympathetic ganglionectomy are equally capable of producing vasodilatation of the collateral circulation.

Most instructive material on the results of sympathectomy performed by the Fellows of the Association of Surgeons of Great Britain and

91. Danielopolu, D.; Aslan, A., and Marcou, I.: La sympathicotomie interlombosacrée dans les troubles trophiques des membres inférieurs, J. de chir. **46**: 657 (Nov.) 1935.

Ireland has been collected, tabulated and analyzed by J. Paterson Ross.[92] Sympathetic ganglionectomy for Raynaud's disease was carried out forty-one times. The operation when technically complete was successful in all cases of Raynaud's disease with mild involvement and in the majority of those complicated by ulceration, but when the disease was present in a severe form accompanied with scleroderma, sympathectomy was a complete failure in eight of eleven cases. The author brings out the interesting fact that scleroderma was not present in any of the patients treated by lumbar ganglionectomy and that this may be another factor in the more favorable results of lumbar as compared with cervicothoracic sympathectomy for Raynaud's disease. The results are expressed in terms of success, improvement or failure, and all patients have been followed for one year, two years or more than two years. The opinion, expressed by the author in another study [93] is reemphasized, i. e., the success of sympathectomy in a person with Raynaud's disease depends almost entirely on the condition of the arterial walls and by recognizing the presence of structural disease it should be possible to avoid the disappointment which follows a faultless operation performed in an unsuitable case. My own experience with Raynaud's disease in its different stages is entirely in accord with this statement regarding the structural element as one of the causes of failure.

The tabulated results of lumbar ganglionectomy in sixty-six cases of thrombo-angiitis obliterans confirms the prevalent impression that intermittent claudication is a symptom which is difficult to relieve. Rest pain, however, and gangrene in an early stage often respond favorably to ganglionectomy. The study of these cases has failed to indicate any clinical picture by which one can forecast the result of the operation. The response of the cutaneous temperature to spinal anesthesia is sometimes helpful, but a poor response must not be regarded as a clear contraindication to ganglionectomy. It is questionable whether the pathologic process can be retarded by the operation. Popliteal thrombosis may develop after the operation and necessitate amputation. Cervicothoracic ganglionectomy was performed in three cases, the operation being successful in two cases but a complete failure in the third case.

The proper selection of patients suffering from Buerger's disease for sympathetic ganglionectomy is still an open question. In my experience remarkable benefit lasting over several years may be obtained, but the preoperative and postoperative conservative treatment must be just as

92. Ross, J. Paterson: The Results of Sympathectomy: An Analysis of the Cases Reported by Fellows of the Association of Surgeons, Brit. J. Surg. **23**:433 (Oct.) 1935.

93. Ross, Paterson J.: The Recognition of Structural Changes in the Arteries in Raynaud's Disease, St. Barth. Hosp. Rep. **68**:121, 1935.

meticulous as if the operation had not been undertaken at all. Analogy with the results of the surgical treatment of duodenal ulcer readily suggests itself.

Twenty-six patients with impairment of the circulation in the legs following infantile paralysis were treated by lumbar ganglionectomy, and one patient was treated by cervicothoracic ganglionectomy. In a group of nine cases in which the affected limb was merely cold and cyanosed, the operation was eminently successful, both the color and the temperature of the affected limb being restored to normal. In a group of seventeen cases in which there was ulceration, thirteen legs were successfully treated and two were improved and in two instances the operation was a failure (with persistent ulceration in one case and pain necessitating amputation in the other). One case was reported in which lumbar ganglionectomy had been performed for "trophic" ulceration of the leg accompanying spina bifida. The operation was unsuccessful.

Lumbar ganglionectomy was performed in fourteen cases for "erythrocyanosis frigida." This condition, which is described by the author as showing characteristic patches of mottled red and blue discoloration, thickening of the tissues and occasional ulceration, affects the legs of young women. The reports are satisfactory, but in my clinic such a condition is usually regarded as being on an endocrine basis, and at least a trial with active endocrine preparations is attempted. The hard edema does not subside after sympathectomy; the limb seldom recovers its natural shape.

In nine cases of causalgia sympathectomy afforded remarkable relief from pain. Sympathectomy was undertaken only after the pain had persisted in spite of the removal of any local stimulus. The most suitable cases of sympathectomy seemed to be those in which the pain was accompanied with vasomotor phenomena such as cyanosis and flushing of the skin, oversensitivity to changes in temperature and an excessive secretion of sweat. Any gross cause of local nerve irritation should be removed previously.

In the conclusion of this most significant analysis, Ross states that sympathectomy is undertaken not for the purpose of excising diseased structures but for the purpose of rectifying functional disorders in an organ the activity of which is controlled by sympathetic impulses. If Sunder-Plassmann's [81] histologic observations are confirmed by others, at least in some instances diseased or irritated ganglions are being removed by these operations.

Harris and MacDonald [94] have continued their study on the rate of growth of a paralyzed poliomyelitic extremity after sympathectomy.

94. Harris, R. I., and MacDonald, J. L.: Effect of Lumbar Sympathectomy on Growth of Legs Paralyzed by Anterior Poliomyelitis, J. Bone & Joint Surg. **18**:35 (Jan.) 1936.

They state that a prolonged increase in the blood supply of a growing child can result in acceleration of the growth of the extremity. Thus they noted an increased rate of growth in a child following removal of the left lumbar sympathetic chain for Hirschsprung's disease. Even in poliomyelitic limbs the rate of growth can be accelerated. The shortness which follows paralysis of the lower extremity is due to the loss of accessory factors which normally enhance the basic rate of growth from the epiphysial line, such as contractions of the normal musculature and the maintenance of a normal blood supply. The factors which favor a good result are (1) paralysis limited to one extremity, (2) a moderate degree of paralysis and (3) an early operation, preferably at the age of 6 years or less, which results in a persistent increase in the circulation. This is obtained by ganglionectomy but not by ramisection.

Valdoni [95] reports on two patients suffering from Raynaud's disease in whom cervicothoracic sympathectomy resulted in complete failure but finally the administration of filtered urine of pregnant women diminished the number and intensity of the attacks. In analyzing the two cases it becomes apparent that (1) both patients were in the third stage of Raynaud's disease and (2) in both cases the operation was postganglionic section of fibers to the upper extremity, which is known to give rise to recurrences frequently.

AMPUTATION

Major and minor amputations still play an important part in the surgical treatment of peripheral vascular disease. McKittrick [96] published interesting figures on the percentage of amputations for thromboangiitis obliterans, arteriosclerosis and diabetes. Of fifty-three patients with thrombo-angiitis obliterans, 32 per cent had a minor and 26.4 per cent had a major amputation, only three being subjected to sympathetic ganglionectomy. Of fifty-five arteriosclerotic patients, 9.1 per cent had a minor and 54.5 per cent needed a major amputation. In the group of two hundred and fifty-three diabetic patients 2.7 per cent had a minor and 46.3 per cent had a major amputation. The percental decrease of minor and the increase of major amputations from the first group to the third group is illuminating. The author's radical surgical approach in cases of Buerger's disease is in contrast to the statement of Samuels,[61] who never has to amputate in cases of Buerger's disease except to remove massive gangrene. In cases of progressive extension of gangrene with rapidly spreading infection and destruction of much weight-bearing tissue an early, high amputation is advocated by McKittrick,

95. Valdoni, P.: Osservazioni cliniche in due casi di morbo di Raynaud recidivati a operazioni sul sympatico, Policlinico (sez. chir.) **43**: 32 (Jan.) 1936.

96. McKittrick, L. S.: Indications for Amputation in Progressive Arterial Obliteration of the Lower Extremities, Ann. Surg. **102**:342 (Sept.) 1935.

preferably the Gritti-Stokes procedure. The mortality following amputation can be steadily decreased; it was around 15 per cent in this series. The basic unavoidable mortality following amputation in such a group is 5 per cent.

With newer technical procedures such as those of Beverly Smith [97] and Callander [98] the danger of shock, the exposure of large surfaces of muscle and the opening of numerous fascial planes inviting ascending infection have been minimized. Amputation is becoming a delicate operation requiring clean anatomic dissection, avoidance of unnecessary trauma and the giving of due consideration to proper weight bearing and painless, freely movable scars. A patient with a well fitted, suitable artificial limb may well be of higher economic efficiency than a patient whose leg has been "saved" but who is a bedridden and painridden invalid, never sure of freedom from future danger. The internist who submits a patient at the terminal stage of a vascular disease for operation and the surgeon who recognizes no conservative measures for the treatment of peripheral vascular disease should give way to a closely cooperating unit of men actively engaged in the treatment of peripheral vascular disease. Improvement in statistics invariably follows such group study.

97. Smith, Beverly C.: Amputation Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene, Arch. Surg. **27**:267 (Aug.) 1933.

98. Callander, C. L.: A New Amputation in the Lower Third of the Thigh, J. A. M. A. **105**:1746 (Nov. 30) 1935.

News and Comment

The Sixth Annual Convention of the Biological Photographic Association will be held in Boston (Hotel Lenox) from September 24 to 26. An invitation is extended to scientists to attend. There will be an exhibition of photographs from all over the country and of the most modern equipment and supplies.

Active membership is open to those whose duties include biologic photography. Any one who is interested in such photography may become an associate member. The annual dues, including a subscription to the journal, are $3.00. Further information may be procured from the secretary, Miss Anne Shiras, the Magee Hospital, the University of Pittsburgh, Pittsburgh.

The following papers are included on the program: "Ultra Slow Mercuric 'Spark' Motion Picture Apparatus," by Dr. H. E. Edgerton, of the Massachusetts Institute of Technology, Boston; "Print Quality," by Ralph P. Creer, of the Veterans Administration, Hines, Ill.; "Infra-Red Photography," by Leo C. Massopust, of the Research Laboratory of the Marquette University School of Medicine. Milwaukee; a paper on optics, the title to be announced, by Prof. A. C. Hardy, of the Massachusetts Institute of Technology, Boston; "Orthostereoscopic Photography," by Mr. Henry F. Kurtz, of the Scientific Bureau, Bausch & Lomb Optical Company, Rochester, N. Y.; "Motion Pictures as an Aid in Teaching Entomology," by Dr. C. T. Brues, of the Department of Biology, Harvard University, Cambridge, Mass., and "Experimental Motion Pictures of the Larynx," by Leonard Julin, of the Mayo Clinic, Rochester, Minn.

The association publishes a quarterly journal. It circulates its print exhibition as a traveling salon, and it has a series of instructive illustrated albums for the use of its members.

Book Reviews

Thérapeutique hydro-climatologique des maladies du foie et des voies biliaires. By Paul Carnot, Maurice Villaret and René Cachera. Paper. Price, 20 francs. Pp. 152. Paris: Masson & Cie, 1935.

The tone of this tract is set at the start when it is remarked that the chief benefit from hydrotherapy lies in the realm of the mild functional insufficiencies of the liver that cannot be detected by laboratory tests. The discussion of the indications for this form of therapy proceeds from this point. In general, it seems that in the "pre-" states, such as *l'état pré-lithiasique* and *l'état pré-cirrhotique*, the condition is most amenable to hydrotherapy, while this form of treatment is contraindicated in cases of frank cirrhosis, lithiasis and cholecystitis. An exception is made in the case of mild hepatitis. The diagnosis of these conditions that may improve with hydrotherapy is too generalized to be of value.

The section devoted to an explanation of the "cure" is vague. The data reported impresses one by the lack of controlled experiments. Throughout this section generalities relating to the acid-base equilibrium, p_H, choleresis, glycoregulation, antianaphylaxis and cholesteremia follow one another indiscriminately in profusion. There are no chemical data of any kind listed to illustrate the benefit of the "cures." The section on climatology and disease of the liver is regrettably brief; one is curious to know why an elevation of from 600 to 1,000 meters has a sedative and regulative action on the neurovegetative equilibrium, especially in persons with vagotonia.

The final section is devoted to an illuminating description of the characteristics of the water and the therapeutic benefits of various resorts. It is interesting to note that the largest mineral content of the drinking spas is about 8 Gm. of sodium bicarbonate per liter, and the daily consumption seldom exceeds 2 liters. The authors admit that there are springs elsewhere as good as those in France. The whole volume has a resemblance to a catalog of proprietary remedies.

Das Ventrikologram. By Erik Lysholm, assisted by Bertil Ebenius and Hans Sahlstedt, of the Röntgeninstitut, Seraphimerkrankenhaus, Stockholm. **Part I: Röntgentechnik.** Acta Radiologica, Supplementum XXIV, 1935.

This valuable work of some seventy-five pages is a definite contribution to ventriculography. The authors have had at their disposal the material of Professor Olivecrona and Professor Antoni at Seraphimerlasarettet in Stockholm. During the past ten years they have studied almost 2,000 patients pneumographically and 112 by the use of iodized oil. Of the total number, 340 were considered to be normal and form the material of this well illustrated report, which gives in detail the technic used in this important clinic.

The authors state: "In addition to the more conventional projections, many special methods were developed for the study of the various parts of the ventricular system. Thus, routine roentgenography was gradually supplanted by a technic which individualized each case." Variations in the amount of air injected, the position of the subject's head and the angle of projection brought out with considerable clearness the particular parts of the ventricular system under suspicion. Twelve such combinations are described and are illustrated with reproductions of the roentgenogram obtained in each case. In ten of the twelve methods the patient is placed in the horizontal position either prone or supine, and the neck is flexed or extended in order to bring different portions of the ventricular system uppermost. Sagittal, half-axial and lateral projections are utilized. Lateral and sagittal projections taken with the patient in the upright position are also utilized.

The results obtained for the normal subject are convincing. A degree of detail has been achieved which is often impossible to obtain with other methods, and the flexibility of the technic allows the concentration of attention on the suspected areas. The half-axial projections seem particularly revealing. One awaits with interest the publication of the results obtained by these methods in the study of pathologic material.

Russell A. Hibbs: Pioneer in Orthopedic Surgery, 1869-1932. By Dr. George M. Goodwin. Price, $2. Pp. 136, with 15 illustrations and 2 diagrams. New York: Columbia University Press, 1935.

So often even the best type of doctor lives his life, does what he can to be useful, dies and is soon forgotten, except for a more or less perfunctory death notice, that it is a comfort to read a sympathetic medical biography written by a man's friends.

The author of this book has painted a pleasant portrait of Dr. Hibbs—a fine doctor; a tall, rangy, upstanding, colorful, ingenious Kentuckian who came to New York as a youngster, fought his way unaided to the front ranks of American orthopedic surgery and eventually became professor of orthopedic surgery at Columbia University. During his lifetime he made many friends, vastly enjoyed being alive and contributed definitely to the advancement of his specialty.

His story is told briefly by Dr. Goodwin. Dr. Karl Vogel's tribute, which appeared originally in the *New York Times*, is reprinted. Dr. Samuel W. Lambert has written a delightful chapter on Dr. Hibbs as a sportsman—an interesting characteristic to emphasize, for so often in thinking of a doctor one forgets that affectionateness, humor and skill in the art of friendship do more to keep memories alive than does professional ability.

The remainder of the book is comprised of Dr. Hibbs' four most significant contributions to orthopedic surgery, entitled: "Lengthening the Tendo Achillis" (1900), "An Operation for Stiffening the Knee Joint" (1911), "An Operation for Progressive Spinal Deformities" (1911) and "A Preliminary Report of Twenty Cases of Hip Joint Tuberculosis Treated by an Operation Devised to Eliminate Motion by Fusing the Joint" (1926).

Those who knew Dr. Hibbs will be glad to own this little volume, and others will be glad of an opportunity to become acquainted, even vicariously, with so staunch a character.

Studies on Bone Marrow from Sternal Puncture. By Nils Göran Nordenson. From the IV Medical Service, St. Erik's Hospital, Stockholm, Sweden. Pp. 204, with 8 colored plates. Stockholm: Börtzells, Esselte, 1935.

As the foreign literature is becoming replete with articles concerning the examination of bone marrow aspirated from the sternum for biopsy, a comprehensive review of the subject in English is welcome. This lengthy monograph, covering the literature to the time of its publication (368 items in the bibliography) and incorporating the author's observations made in over three hundred biopsies, falls short of excellency. Its very completeness encumbers its clarity. The hematologist will discover material of definite value but will find the reading laborious. In addition to the twenty-one errata listed, there are many typographic errors. It is difficult to correlate the author's data, as the case protocols and the tables of data on the peripheral blood and on the bone marrow are grouped separately; also, the patients are referred to in the tables by number rather than by diagnosis. The complexity of hematologic nomenclature is allowed to "run riot," although the author describes carefully each type of blood cell used in his differential counts. The selection of normal patients (sex not indicated) may be criticized, as fourteen of thirty-nine patients had red blood cell counts below 4,500,000, and only six had counts above 5,000,000. The hemoglobin values should

be given in grams per hundred cubic centimeters rather than in percentages. All cases of anemia in which a specific diagnosis of pernicious anemia was not made are classed as cases of secondary anemia, so this group includes an extremely heterogeneous collection. The colored plates are excellent. In spite of the many faults in presentation, this work is a valuable contribution to hematology.

Initiation à la pathologie digestive. By P. Harvier. Price, 22 francs. Pp. 162. Paris: Masson & Cie, 1935.

This book is intended primarily for the medical student as an introduction to clinical gastro-enterology, but it merits the attention of his instructor as well. The transference of the student's preclinical knowledge from the laboratory to the patient requires a simple, concise yet thorough presentation. The author never loses sight of this objective.

Disturbances of the digestive tract are treated in the light of alterations of the gastro-intestinal physiology. Without minimizing the physiologic solidarity of the digestive functions, the author has divided his text into a consideration of motor, sensory and secretory disturbances. Particular stress has been placed on the importance of the patient's history, although physical and laboratory findings are adequately considered. Roentgenologic findings are described, typical films being shown, and are considered a definite aid to the student in completing his mental picture of the clinical features of certain conditions.

Some of the author's statements are necessarily dogmatic. The discussion of the physiology of the digestive juices is incomplete, and the almost entire disregard of pathologic conditions of the liver, gallbladder and bile-duct seems inadvisable. Open to grave criticism is the unqualified suggestion that a preparation of barium be given by mouth as an aid in the diagnosis of intestinal obstruction. However, the author has handled a difficult assignment in a most efficient manner.

Infant Nutrition. By W. McKim Marriott, M.D., Professor of Pediatrics, Washington University School of Medicine. Second edition. Price, $4.50. Pp. 431, with 27 illustrations. St. Louis: C. V. Mosby Company, 1935.

The first edition of this book appeared in 1930 and was received kindly. Every one knew the abilities of the author and felt sure that any volume on infant nutrition from his pen would be worth reading. Therefore the reviews, on the whole, were favorable. *The Journal of the American Medical Association* (**95**:1448 [Nov. 8] 1930) stated "in the brief period since it was first made available, the book has received an extraordinary popularity."

There were certain faults in the book, generally admitted, the most serious being its typography. The size and shape were wrong; the paper was rough rather than smooth so that the printing appeared to be indented rather than standing out, and, on the whole, anatomically, there were several undesirable features. All these have been eradicated.

The second edition of "Infant Nutrition" is better printed and of far more attractive appearance than its predecessor. It has been revised, added to and subtracted from for the sake of improvement. It fully deserves the popularity and praise which no doubt it will again acquire.

Beiträge zur Pathogenese und Epidemiologie der Infektionskrankheiten. By Prof. Dr. med. H. A. Gins. Price, 5.50 marks. Pp. 127, with 6 illustrations. Leipzig: Georg Thieme, 1935.

A brief summary of some of the fundamentals of infection and immunity is given for the benefit of the general practitioner or student not specially conversant with the subject. The exposition is clear and simple and makes a continuous story, not interrupted by too many references to the literature.